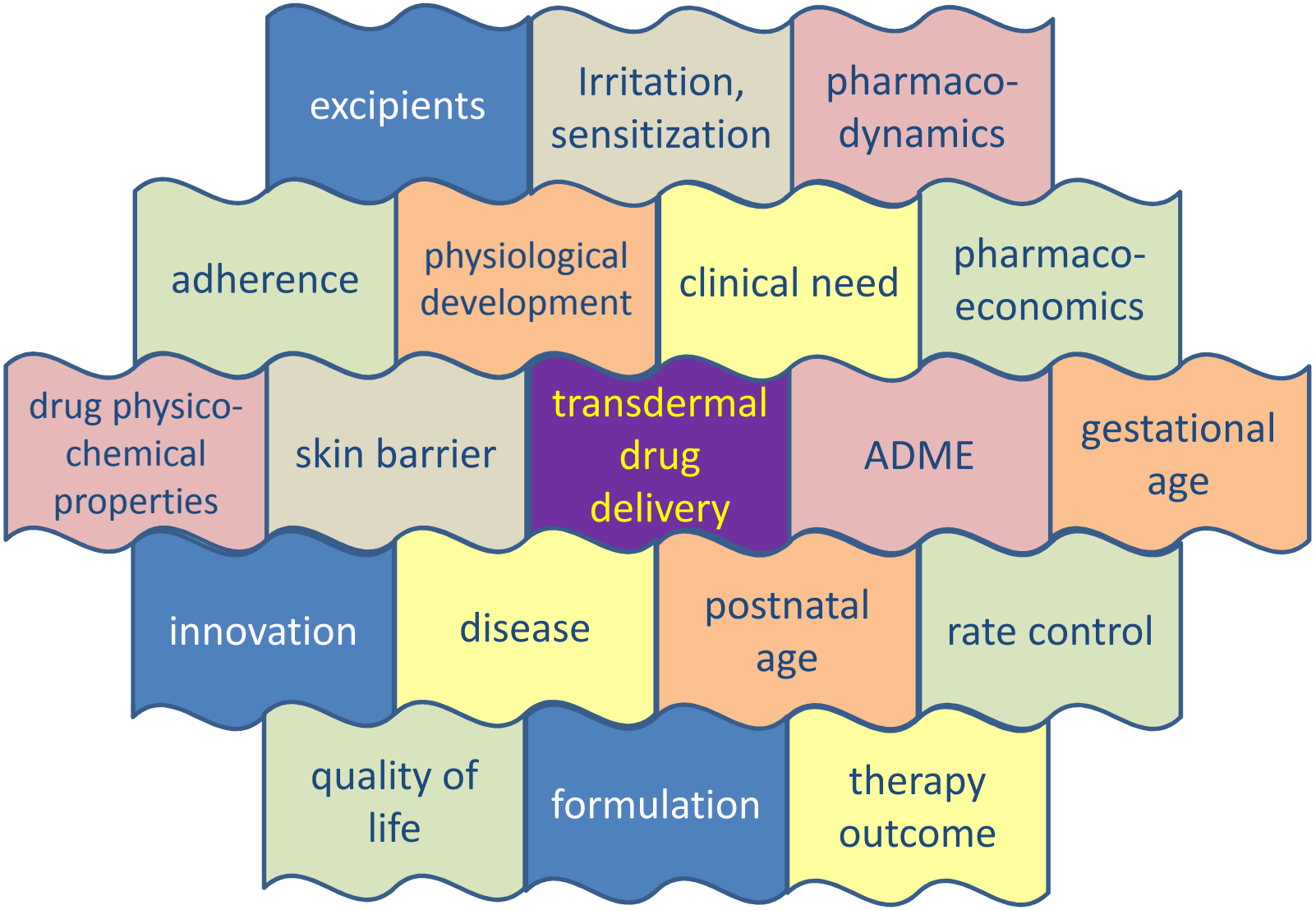
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postnatal age
rate control
quality of life
formulation
therapy outcome

Effective use of transdermal drug delivery in children

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Abstract

Transdermal administration offers a non-invasive and convenient method for paediatric drug delivery. The competent skin barrier function in term infants and older children limits both water loss and the percutaneous entry of chemicals including drugs; but the smaller doses required by children eases the attainment of therapeutic concentrations. Transdermal patches used in paediatrics include fentanyl, buprenorphine, clonidine, scopolamine, methylphenidate, oestrogens, nicotine and tulobuterol. Some patches have paediatric labelling supported by clinical trials whereas others are used unlicensed. Innovative drug delivery methods, such as microneedles and sonophoresis are being tested for their safety and efficacy; needleless injectors are primarily used to administer growth hormone; and two iontophoretic devices were approved for paediatrics. In contrast, the immature and rapidly evolving skin barrier function in premature neonates represents a significant formulation challenge. Unfortunately, this population group suffers from an absence of approved transdermal formulations, a shortcoming exacerbated by the significant risk of excessive drug exposure via the incompletely formed skin barrier.

Keywords: transdermal drug delivery, transdermal patches, paediatric dosage forms, premature neonates, iontophoresis, skin, stratum corneum.

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1. Introduction

The topical and transdermal routes of administration offer some clear and specific advantages for drug delivery. Topical delivery allows targeting of the drug to the local area minimizing systemic exposure; topical formulations usually contain anti-inflammatory, anti-histaminic, antifungal, antiseptic, and analgesic drugs incorporated into creams, ointments, gels, sprays and, less frequently, patches. Transdermal drug delivery (TDD), the object of this review, aims to provide effective systemic concentrations for central, rather than, local effect and is applicable to different therapeutic areas. TDD offers a non-invasive approach to avoid the first-pass effect, and can sustain plasma levels within the therapeutic window for extended periods. Transdermal patches are usually well accepted, easy to apply and represent a valuable alternative when oral administration is difficult (e.g., patient cannot swallow, or is in a coma) or may result in erratic absorption (nausea, vomiting, etc.) [1]. While these advantages are of general interest for the paediatric population, neonates and preterm infants would benefit particularly from a non-invasive route of drug administration and an alternative to oral and intravenous delivery [2]. Unfortunately, the effective barrier properties of the skin mean that TDD is not suitable for all drugs and only those with appropriate physicochemical, pharmacokinetic and pharmacodynamics properties are candidates for delivery across the skin [1, 3]. All drugs available in commercial, passive patches are highly potent, have molecular weights less than 500 Da, and log P (P=octanol/water partition coefficient) values typically between 3-5 [3]. While newer delivery methods such as iontophoresis, needleless injectors and microneedles expand the range of drugs administrable, by easing the constraints related to drug polarity, charge and size, the doses deliverable across the skin remain small. Conveniently, because younger children require smaller doses than adults, it is conceivable that some drugs could be delivered transdermally for paediatric but not for adult use.

Human skin is responsible for several functions including photoprotection, thermoregulation, hormonal synthesis, sensory perception, and immune and barrier functions [4, 5]. Among these, barrier function is the most relevant to drug absorption and not surprisingly, many enhancement techniques have been examined to overcome this challenge [1, 6]. Nevertheless, it is important that the normal functioning of this organ is not disrupted severely because of its key role in survival. The majority of techniques developed

to enhance skin transport have been tested in adult human skin or in animal models [1, 6]. A key question, therefore, is the extent to which “paediatric skin” is represented by these models and whether the knowledge obtained from these models can be transferred and exploited for the benefit of the paediatric population. Importantly, while the latter represents a heterogeneous group of individuals; from the standpoint of the skin barrier function and transdermal absorption, it divides (to all intents and purposes) in two large parts: (1) all children, including neonates born at full-term, whose skin is functionally indistinguishable from adult skin, and (2) preterm neonates who have a thinner and dysfunctional epidermal barrier.

A premature neonate born at ~ 25 weeks gestational age (GA) with very low weight (<0.75 kg) has a very fragile skin which can easily tear; infants born at 30-31 weeks GA and weighing 0.75-1.25 kg have a more resilient, although still immature, skin; finally, the skin of infants born from ~36 weeks GA (1.2-2.0 kg) will be almost as tough and functional as that of full-term new-borns [4]. Premature neonates are obviously the most challenging group concerning transdermal drug administration. Despite significant progress, the relationship between skin absorption, GA and post-natal age (PNA) in this population is insufficiently characterized, making it difficult, if not impossible, to modify drug input in response to not only the rapidly evolving skin barrier function but also to the drug dose requirements (which also increase with PNA); in addition the situation is likely to be further complicated by other underlying developmental and disease issues. Information about the criteria for formulation selection is also missing; for example, whether a patch adhesive is suitable for fragile premature skin, or the potential risk associated with the unexpectedly high absorption of an excipient. While the remarkable immaturity and poor barrier function of pre-term infant skin is universally recognized, there has been debate about the point at which the skin of term infants gains adult functionality. The next section summarizes the key issues and deals more specifically with the development of the skin barrier function.

Importantly, while permeation across the stratum corneum (SC) or outermost layer of the skin, constitutes the rate-limiting step for the skin absorption for most chemicals, the overall absorption process can be modified by other factors not related to the skin barrier maturation (including occlusion, thickness of applied formulation, area of application versus body surface area); furthermore, drug response and toxicity are also determined by

pharmacokinetics and pharmacodynamics which change within the paediatric population and may be quite different from those in adults. To illustrate this point, the skin represents ~13% of the body weight of a pre-term infant but only 3% of that of an adult [7]; the area and site of application of a transdermal patch may have a dramatic impact, therefore, on the safety and efficacy of a treatment in neonates [2, 8].

2. The development of skin barrier function.

The differences between infant and adult skin physiology, as well as the development of skin functionality, including the effects of GA and PNA on transepidermal water loss (TEWL), skin surface pH, skin hydration, skin electrical properties, skin structure and roughness and natural moisturizing factor (NMF) abundance, have been recently and extensively reviewed [5, 7, 9-10].

The development of skin structure from the embryo until birth was comprehensively reviewed by Hardman et al., [10]. Briefly, at 4-5 wk GA the ectoderm of the embryo is covered by the periderm; epidermal stratification starts around 8 wk GA, and the development of skin appendages around 12 wk GA [4, 5]. The periderm acts as the interface between the amniotic fluid with the developing epidermis prior to SC formation; later the periderm sheds to become part of the vernix caseosa at 15-20 wk GA. The effects of GA and PNA on the histological development of the epidermis were reported in 169 (24-40 wk GA) infants aged from a few hours to 1 year old [11]. The thickness and number of epidermal cell layers, the degree of undulation of the dermo-epidermal junction, and the SC thickness increased clearly with GA in children who had died within 7 days of birth; both the SC and the dermo-epidermal undulations were barely perceptible until 34 wk GA. It was suggested later that, while functional maturation of the SC starts around the 24 week of gestation, a well-defined SC is not visible before 34 wk GA. Indeed, SC formation has been observed at 22 wk GA in the epidermis of the head/scalp and in palmar/plantar skin and, at 25 wk, over the rest of the body [12]. According to some, a functional skin barrier appears regionally, with the inter-follicular barrier forming at 20-21 wk GA on the head and at 23-24 wk GA on the abdomen. The barrier appears to develop between 20-24 wk GA in a patterned manner, starting at specific initiation sites but also around emerging hair follicles. The link between epidermal differentiation and skin permeability during foetal development was

characterized for 55, 75, 84, and 96 d GA and 115 d (full-term) swine foetuses [13]; the permeability to arecoline decreased significantly for the 96 d GA group corresponding to the visual appearance of the SC and the partially keratinized epidermis. Notably, the permeability of ionized arecoline across skin from 96 d GA and older foetuses was significantly less than that of the unionized species, an observation consistent with the development of a lipid barrier.

It is now generally accepted that the inward percutaneous penetration of chemicals is correlated to the transepidermal water loss (TEWL) [14]. Further, the link appears to be maintained throughout the human-life span. The topical absorption of hydrocortisone in a group of 3 children and 6 adults (3 to 52 years) with widespread dermatitis produced a significant correlation between TEWL and the post-application plasma levels of cortisol irrespective of age [15]. It is therefore not surprising, that TEWL has been extensively used both to characterize the degree of skin barrier function and maturity and to predict chemical absorption.

The earliest studies of insensible water loss (IWL) aimed to develop adequate support for pre-term neonates, in particular, to maintain fluid balance and to determine the effect of different care techniques on water loss. Weight loss was used as an indirect measurement of IWL accounting therefore for both water loss through the skin areas and via respiration [16] (although, according to some [17], IWL accounts for ~90% of the weight loss). As early as 1972, it was hypothesized that immature skin was the reason for the high IWL observed in a cohort of 30 infants of 23-36 wk GA [17]. Because IWL is modified by additional factors such as basal metabolic rate, ambient and body temperature, relative humidity, neonate activity, and phototherapy, the results from different studies must be carefully compared [18]. In fact, important effects of radiant therapy, incubators, bililights and radiant heaters on IWL (weight loss) and TEWL have been demonstrated [19-20]. However, despite these additional contributing factors, a clear inverse relationship between body weight and IWL (weight loss) was reported for 54 healthy pre-term infants [21]; additionally, it was shown that IWL decreased with PNA for infants with birth weights of ≤1.5 kg, a correlation interpreted as a sign of skin function maturation. One of the earliest explicit links between skin barrier function development and TEWL was a study in 28 infants of 2-9 d PNA and 26-41 wk GA [20]. TEWL was significantly higher for premature infants born at 27-29 weeks GA;

it was also observed that older preterm and normal term infants had similar TEWL, which again suggested fast, post-natal skin maturation for the pre-term group.

Significant progress was then possible due to the development of “evaporimeters” that directly measured water vapour at the skin surface, and numerous investigations with this apparatus then confirmed previous findings [22-23]. TEWL (evaporimeter) was inversely and exponentially related to GA for both low and normal weight infants during the first 4 weeks after birth [24]. Even when directly measured at the skin surface, the TEWL in term and pre-term infants can be modified by multiple factors including body temperature, ambient humidity, physical activity, maturity, nutritional status at birth, cold stimulation, GA and PNA; the contributing factors can be changes in skin structure, sweat gland function and activation, skin blood flow, skin hydration, basal metabolic rate, and total body water [16, 23]. The use of radiant warmers approximately doubles IWL (measured as weight loss) of infants [18]; the use of heat shields reduces this effect [25]. Administration of prenatal steroids (to the pregnant mother) does not affect foetal barrier maturation; in contrast post-natal parenteral steroid administration inhibits this process [26].

The key findings of the initial measurements of TEWL using evaporimeters have been summarized [27]. It is worth noting that some work involved determination of TEWL at a specific site on the body, while others average measurements made at (e.g.,) three locations to inform total fluid loss [27]. Clearly, in terms of using TEWL as a marker of skin permeability in general (including to drugs), the individual assessments at specific skin sites are more useful.

The effect of GA on percutaneous absorption in preterm infants was nicely demonstrated by a method to assess skin permeability based on the blanching response observed following topical application of Neo-Synephrine® aqueous solution [28]. The blanching effect was visible in all 28-34 wk GA infants but was lost beyond 21 d PNA; the response was delayed and of lesser magnitude in infants born at 35-37 wk GA; and there was no blanching effect in infants born at 38-42 wk GA. A further study linked TEWL with drug absorption in 70 new-borns classified in four GA groups (Fig.1) [29]. The vasoconstriction observed after topical application of phenylephrine was minimal for infants of ≥37 wk GA who also showed the lowest TEWL (< 10 $g.h^{-1}.m^{-2}$); infants born at 33-36 wk GA, with a TEWL slightly higher than

the previous group, showed a mild response which became less marked after ~1 wk PNA (and corresponded with a drop in TEWL); a higher TEWL and an increased response to phenylephrine was observed for infants of 30-32 wk GA and, in this case, TEWL fell to normal values and the response disappeared by 2 wk PNA; finally the most immature infants (<30 wk GA) showed the largest blanching response and the highest TEWL which again decreased to normal two weeks after birth [29]. Thus, a striking correlation between blanching effect, a surrogate marker for drug absorption, and TEWL was observed. Parallel measurements found an increased blanching response in skin sites with increased TEWL caused by barrier perturbation upon removal of adhesive tapes and medical rings. The transdermal absorption of benzoic acid was elevated in pre-term infants and declined over three weeks to "normal" levels based on results in adults [30]. The rapid changes in TEWL and chemical absorption observed post-natally in pre-term infants are consistent with the histological changes previously reported [11]. For example, the skin of infants born at 24-30 wk GA shows a significant increase in the number of epidermal cell layers and develops a well-formed SC over a 16 week post-natal period; however, little development of dermo-epidermal undulations was observed.

By the end of the 1980s, the emerging message was that TEWL and percutaneous absorption across the skin of full-term neonates were similar to those in adults, while premature infants (less than 34 wk GA) had an incomplete skin barrier and were vulnerable to dehydration and infection, and to the dermal uptake of potentially toxic substances. An alternative point of view was that premature skin offered an accessible and non-invasive route of drug delivery for this population, enabling the facile administration of therapeutic doses. However, the rapid, functional development of premature infant skin (often evolving to a mature barrier after ~2 wk PNA) confounds this potential drug delivery opportunity: how does one develop methods to predict the level of skin maturity and permeability for a specific new-born, and then design formulations, which can safely deliver drugs with the required rate and extent of absorption to this rapidly evolving "moving target"?

The current advances in postnatal care make it possible for ultra-low birth infants to survive. Skin barrier development was assessed in 23-32 wk GA children using TEWL and impedance spectroscopy [26]. Low-frequency skin impedance increased significantly with barrier development and was inversely correlated with TEWL; i.e., TEWL was highest (60-70 $g.h^{-1}.m^{-}$

^{2}) and low frequency impedance smallest for infants born with the shortest GA and PNA. Barrier function development appeared to accelerate at 200-220 days post-conception, regardless of GA and PNA, and 30 wk GA was identified as a key milestone. Significantly, the very premature infants had not achieved a competent barrier 2-4 weeks after birth; furthermore, in some subjects, a detrimental effect of parenteral steroid administration on barrier function development was observed.

An interesting feature of new-born skin is the vernix caseosa, a film of lipoproteic material with embedded foetal corneocytes that is missing in infants born at less than 28 wk GA [31]. The vernix caseosa is composed of water (80.5%), proteins (8-10%) and lipids (8-10%); cholesterol is the major lipid component followed by free fatty acids (FFA) and ceramides. In contrast, FFA represent the dominant lipid in both post- and pre-natal skin [32]. It is estimated that ~30% of the lipids of the vernix caseosa originate from the epidermis with the remainder coming from sebaceous glands. It has been suggested that the vernix caseosa is shed when the transepidermal lipid barrier is sufficiently developed; hence, its disappearance is used as a mark of foetal maturity [33].

To summarize, it is clear that the SC of pre-term new-borns provides a defective barrier resulting in significantly elevated TEWL. On the other hand, the SC of term neonates provides a competent barrier with TEWL similar to that across adult skin [5]. The competence of the full-term infant skin is supported by considerable research, some as early as 1977 [34] which showed that TEWL and carbon dioxide emission rates across the skin of healthy term infants and healthy adults were comparable.

Differences as a function of body site have also been considered. TEWL was comparable across abdominal, buttock and forearm skin of 13 (8-48 h PNA) new-born term infants and was significantly increased after 1 hour occlusion at the three sites A study on 28 (38-40 wk GA) healthy infants examined 18 body sites and found significant inter-site variability; TEWL was particularly high on the forehead and palm of the hand, elevated on the cheek, upper arm, and sole of the foot, and lower on the abdomen and chest [35]. It is possible that environmental factors (relative humidity, occlusion, effect of diapers) contributed to some of the differences observed.

Recently, an investigation in 1,036 healthy term infants provided the most comprehensive, reference values for TEWL on the arm measured with an open-chamber evaporimeter [36]. The results were normally distributed with a mean (± standard deviation) of 7.06 ± 3.41 $g.h^{-1}.cm^{-2}$, comparable to that of adult skin. The results for 18 late pre-term infants (34-37 wk GA) was rather similar: 7.76 ± 2.85 $g.h^{-1}.cm^{-2}$. It should be noted that open- and closed chamber evaporimeters provide different absolute TEWL readings [37-38], preventing a direct comparison between results obtained with the two approaches; unfortunately, a comparative reference data set is not available for measurements made with a closed chamber evaporimeter.

The link between skin lipids and barrier function has been considered. In 1978 [39], TEWL (resistance hydrometry) and the concentration of skin surface lipids were measured in 40 (3-12 y) healthy Japanese children. TEWL was not modified by age, gender, and weight; on the forearm the values in children (0.23 ± 0.03 $mg.cm^{-2}.h^{-1}$) and adults (0.24 ± 0.02 $mg.cm^{-2}.h^{-1}$) were indistinguishable. Similarly, the amounts of cholesterol on the children's skin (2.84 ± 1.74 $\mu g.cm^{-2}$) and on adult skin (2.44 ± 1.44 $\mu g.cm^{-2}$) were not statistically different; however, the children's skin had significantly less squalene (0.31 ± 0.25 $\mu g.cm^{-2}$) than that of adults (0.74 ± 0.61 $\mu g.cm^{-2}$). The difference in sebaceous lipids, which are not considered as key contributors to barrier function, was explained by the immature secretory activity of the sebaceous glands in children. On the other hand, a clear relationship between the concentration of non-sebaceous lipids and TEWL was observed. Later work found significant differences in the composition of lipids extracted from the epidermis at 14-17 wk and at 20-28 wk GA; the latter group also had less lipids than typically found in adults [40].

While TEWL is essentially the same in adults and full-term infants, other aspects of skin function do change after birth. These differences between infant and adult skin physiology have been reviewed [5, 7, 9] and concern properties such as skin surface pH, skin hydration, skin and SC thickness, desquamation and corneocyte size. Some of these results are based on data from small cohorts and may be difficult to generalise due to differences in methodology and skin sites studied (see [7] for comprehensive details). A comparison between 70 (8-24 months old) children and 30 (25-35 y) healthy women revealed, as expected, that baseline TEWL was the same in both groups; however, skin capacitance (measured with a corneometer) was higher on the volar forearm of children (but not on the

buttocks) than that of adults, and that skin pH was higher in children (5.5 - 5.8) than in adults (4.5 – 5.0) [41]. In healthy, full-term neonates, a decrease (0.3 - 1.1) in surface skin pH, increased desquamation on the face, a smoother skin surface, and an increase in SC hydration were noted during the first 3 months of life [42]. Another investigation also recorded that the skin surface pH fell from neutral to 5.0 - 5.5 within two weeks of birth.

TEWL (evaporimeter), skin hydration (corneometer), skin surface pH, and the Raman confocal microscopy (RCM) profiles of water and natural moisturizing factor (NMF) were assessed in children (1 d - 5 y) and adults [43]. TEWL was similar as expected, while skin surface pH decreased from ~6.0 for new-borns to 5.10 by 5-6 wk, 5.20 at 4-5 y, and to 5.5 in adults (20-35 y). The average area-under-the curve of Raman-assessed NMF levels as a function of skin depth was greatest for new-borns and smallest for the 6 month age group; however, mean AUCs for lactic acid were similar for all ages. Finally, skin capacitance was lowest at birth and highest for the 5-6 wk and 6 m age groups. RCM was also used to show that the skin of infants (3-12 m) has less NMF but a higher water content than adult skin; it should be pointed out that this is one of the few studies to report higher (4-5 fold) TEWL values for 3-12 m children than for adults [44]. According to Hori et al., [45] the skin developmental process over the first year of life differed in the upper thighs with respect to that observed in diaper-covered areas.

It was reported that 36-40 wk GA infants experience an increase in epidermal cell number, and epidermal (but not SC) thickness, and developed a more undulated dermo-epidermal junction from birth until 16 wk PNA [11]. Elsewhere, infant skin has been shown to have smaller corneocytes, faster cell turnover and a thinner SC than adult skin [9]. The latter finding, in contradiction to previous work, may be an artefact of the methodology used which assessed SC thickness from optical sections taken every 3.1 µm, which is close to the difference reported between adult (10.5 ± 2.1 µm) and children's (7.3 ± 1.1 µm) SC thickness [9]. Skin equivalents (SE) from new-born, child and adult foreskin keratinocytes were produced and compared; briefly, those from new-borns had a greater proportion of stem cells (as indicated by K19 expression) and produced a thicker skin (than the adult cells) more quickly. However, once keratinocyte differentiation was induced, the three mature SEs were similar in their histological expression of differentiation markers and in lipid content.

Further, transport of hydrocortisone across SE samples was similar for the three groups, although higher than across foreskin samples [46].

Nevertheless, of all skin physiological properties and their possible development through infancy [7], none has been linked to the percutaneous absorption of chemicals as unquestionably as TEWL. An additional factor, of potential relevance to skin barrier function, is cutaneous blood flow. At birth, capillary loops are only seen in the nails bed, palms and soles, and are not observable in all skin sites until 14-17 wk; furthermore, the development of the cutaneous micro-vasculature is site-dependent [5]. It is believed that adaptation of the dermal microcirculation can take longer in preterm infants, but how exactly that may translate into altered skin absorption has not been deconvolved. This is a complex issue as skin blood flow is modified by ambient temperature, relative humidity and nutrition.

The SC structure and composition, especially that of the intercellular lipids, govern TEWL and play a major role in determining the rate and extent of skin absorption across this barrier [47]. Together with the physicochemical properties of the permeant, SC development defines, therefore, the feasibility of passive topical/transdermal drug delivery and the risks associated with dermal exposure via passive diffusion. On the other hand, the skin appendages (sweat glands, hair follicles) represent important permeation pathways for some alternative delivery approaches, such as iontophoresis [48]. The development of hair in utero and in neonates has been characterized and it has been suggested that an infant is born with a fixed number of sweat glands and hair follicles meaning that the number of annexes per unit area of skin decreases with growth [49]. For example, the follicular density on the scalp of new-born infants has been reported to range from 500 to over 1100 per cm^2; in contrast, in adults, the corresponding values on the occipital scalp have been measured to be only 239 and 292-455 per cm^2 [49-51]. The hair follicle density in adults is significantly lower (14-90 follicles.cm^{-2}) at other body sites, but comparable values are not available for new-borns [50]. More recently, video-dermatoscopy was used to characterize five areas of the scalp in 45 neonates, and identified that two clinical patterns, namely “good hair density” (GHD) and “poor hair density” (PHD) can be present at birth. These groups could be separated by cut-off values for hair density (505 hair.cm^{-2}), hair shaft diameter (0.06 mm), and hair length (2 cm). PHD neonates typically had lower birth weight with ~20% of new-

borns showing widespread thin hair (0.04 mm diameter and 2 cm length) [49]. However, despite the potential impact of these observations on skin permeation, the role of hair density at different body sites in different paediatric groups remains completely uncharacterized.

Likewise, little is known about the importance of other skin annexes on barrier function. Thermoregulation and eccrine gland function does not mature until after term [5, 7, 31]. At 24-29 wk GA it is possible to observe sweat glands with an adult structure, complete with secretory ducts. The appearance and cellular differentiation of the eccrine system is the same in term and pre-term infants; however most >36 weeks GA infants can sweat in response to environmental stimulus on their first day of life whereas pre-term (< 36 weeks GA) cannot [5, 7]. Transdermal electrical potential measurements also suggest that sweat glands are immature in infants of less than 24 wk GA, skin resistance increases with GA and appears to mature around 36 weeks GA [52]. Sebaceous glands, which provide most of the lipids for the vernix caseosa, are visible by the 18th week of gestation but remain hypertrophic for some weeks after birth as a result of maternal hormone exposure [5, 7, 10].

3. Skin absorption: potential for toxicity and for transdermal drug delivery in paediatrics.

3.1 *In vitro* and *in vivo* skin drug absorption studies.

The transdermal delivery of xanthines (theophylline and caffeine) to treat apnoea in premature infants was one of the earliest applications taking advantage of the increased skin permeability in this population. Transdermal administration was considered advantageous and convenient, removing the need for an IV line and avoiding fluid overload, and preventing reduced gut motility and bacterial overgrowth associated with oral administration [53-54]. Evans et al. [55] delivered theophylline sodium glycinate from a 15% w/w gel to 20 infants (26-30 wk GA; 1-20 d PNA; 0.6-1.44 kg weight). Therapeutic drug levels were reached within 9-30 h in children naïve to theophylline. Furthermore, the gels were able to maintain effective drug concentrations in infants who had, up to that point, been receiving an aminophylline infusion. In a similar fashion, the drug was formulated in hydrogel disks and plasma concentrations of theophylline in the therapeutic range were attained and maintained for up to 15 days in 18 (24-30 wk GA) preterm infants [56]. An

inverse correlation was observed between the maximum concentration observed and TEWL; for example, a child with very immature skin and extremely high TEWL (100 $g.m^{-2}.h^{-1}$) developed signs of theophylline toxicity. The pharmacokinetics of theophylline after transdermal administration were investigated in 9 (32-36 wk GA) infants [53]. The mean half-life of the drug as 28.7±6.1 h; however, sub-therapeutic levels of theophylline were attained in this group of older infants. The administration of caffeine monohydrate (18 $mg.g^{-1}$ caffeine base) from an aqueous gel produced good efficacy and was well tolerated in 18 premature (<32 weeks GA) neonates [57]. It was suggested that caffeine treatment would normally no longer be needed by the time that skin barrier function had developed sufficiently thereby limiting the percutaneous absorption of the drug. In another investigation, a caffeine citrate gel was administered to 57 premature (<34 wk GA) infants and resulted in therapeutic levels in 73% of the patients after ~48 h and in 97% within 5 days of treatment [54]. High, but asymptomatic levels were observed in 5 subjects at 48 h, and in 19 infants at 6 days; sub-therapeutic levels were detected in 12 neonates at 48 h. Overall, a significant decrease in the frequency of apnoea episodes was observed [54]. Similarly, the application of a different caffeine gel to 56 preterm (26-34 wk GA) infants produced systemic levels which increased from day 2 to day 10 of treatment, reaching therapeutic efficacy in 48 h [58]. Serum concentrations were better correlated to gestational age than birth weight; high drug levels, although without side effects, were measured for the most immature patients. Nonetheless, despite these early, promising results, neither a theophylline nor a caffeine formulation has been developed for this population; in fact, only the oral and parenteral routes are routinely listed in reference guidelines for the treatment of infant apnoea [59-60].

Although the topical administration of glyceryl trinitrate (GTN) to induce vasodilatation in children and to facilitate access to peripheral veins has been reported [61], a subsequent double-blind study in 23 infants (3 wk-10 y) found the approach inefficient and demonstrated no relation between local drug concentration and venous distension [62]. Case reports have described the effective use of a topical GTN ointment to treat (a) perniosis in a 6 m old boy, who was unresponsive to other therapy [63] and (b) severe tissue ischemia in four neonates [64], but neither publication has provoked any further activity in this area.

As drug dose requirements in children are typically lower than those in adults, the transdermal route of administration may be more feasible in paediatric subjects [59,65]. Nevertheless, some targets remain unrealistic. For example the daily, neonatal dose range for paracetamol is 10-30 $mg.kg^{-1}$ [59,66], which cannot be achieved across the skin. Even when the target delivery rate is more reasonable, careful consideration of the formulation (and, in particular, the use of penetration enhancers) is necessary to minimise the potential for skin irritation. This raises the important question as to how the feasibility of transdermal drug administration in infants may be assessed pre-clinically? Clearly, *in vitro* permeation experiments using adult human skin are possible, but the better barrier function (relative to premature neonate skin) may lead to an erroneous conclusion. Likewise, there is little evidence to support the use of an animal model (even those with known higher skin permeabilities than man) as the relative permeability with respect to infant skin is not known. Ideally, the best *in vitro* model would be neonatal skin, but the availability and procurement of such tissues pose real problems for obvious reasons. However, there have been some reports describing drug transport measurements across skin samples obtained from infants post-mortem. For example, the *in vitro* skin permeation of phenobarbital, which is used to treat status epilepticus, neonatal seizures, and neonatal abstinence syndrome, has been investigated [67]. Unsurprisingly, drug flux was higher across skin sourced from the most immature infants. Phenobarbital penetration decreased with increasing GA and, from 37 weeks, it was very similar to that across adult skin (Fig.2-3). While it was suggested, on the basis of the results obtained that a therapeutic dose could be delivered transdermally to pre-term and term neonates, the formulation used (39 $\mu L.cm^{-2}$ of a 2 $mg.mL^{-1}$ of phenobarbital in ethanol) was obviously sub-optimal.

The *in vitro* delivery of the analgesic diamorphine across skin from premature neonates also showed a clear inverse relationship with the donor GA (Fig.2) [68]. Despite the simplicity of the formulation, it was concluded that a 2 cm^2 patch could be of therapeutic use. It was noted that the time required to attain the steady state would be greater for paediatric patients for whom drug elimination pathways are still immature. While the authors of this work suggested that this problem could be solved with an IV loading dose, the current state-of-the-art suggests that iontophoresis can achieve the same objective and render the entire therapy completely non-invasive.

The increased skin permeability of the preterm population also offers an opportunity for non-invasive sampling [69]. An initial investigation involved the transcutaneous collection of theophylline and caffeine in 33 (25-34 wk GA; 2-89 d PNA) infants on theophylline therapy [70]. The 2.54 cm^2 collection systems were composed of 3% agarose, 5% activated charcoal and a 92% salt solution, and were applied for either 4 or 12 hours. Both drugs were detected in the patches but, while the outward fluxes were related to the corresponding plasma levels and post-conception age, they were poor predictors of individual concentrations. The potential of iontophoresis [71] to improve transdermal sampling was later tested and, in this case, tape-stripped pig skin was used as an *in vitro* model for premature skin (see below). Iontophoresis increased and significantly accelerated extraction of caffeine and theophylline compared to passive diffusion across intact skin but showed little benefit when the SC was absent. Unfortunately, the drug extraction flux as a function of its subdermal concentration across skin with intermediate barrier function was not reported.

3.2 Unwanted skin absorption and potential for toxicity.

Concerns about the undesirable systemic absorption of actives and excipients have focused primarily on antiseptics and other topical treatments routinely applied to new-born and, more particularly, preterm infants. The risk of systemic exposure has to be carefully balanced against the need for effective skin disinfection, which is essential to reduce the incidence of infections in new-borns, especially in premature infants who are often subjected to multiple invasive procedures. The potential for undesirable chemical skin absorption in neonates is historically illustrated by hexachlorophene, an antibacterial that was later withdrawn due to safety concerns [72]. Similarly, topical iodine-based disinfectants have also been withdrawn [73]. For example, their use was associated with hypothyroidism in 4 infants (average 37 wk GA) with spina bifida, a side-effect attributed to excessive iodine absorption from antiseptic dressings (povidone iodine 10%) [74]; another study in 30 (26-30 wk GA) infants found increased levels of urinary iodine and some effects on thyroid function [75]. A recent systematic review [76] concluded that topical exposure of preterm infants to iodine (<32 wk GA) leads to thyroid dysfunction. Similarly, the use of alcohol-based products in pre-term infants can cause serious harm as illustrated by the case of a 27 wk GA whose skin was cleaned with methylated spirits (95% ethanol; 5% wood nafta

which contains a minimum 60% methanol); post-mortem blood samples (18 h after exposure) revealed concentrations of ethanol and methanol of 2.59 $mg.mL^{-1}$ and 0.26 $mg.mL^{-1}$, respectively [77].

Chlorhexidine (CHD) was subsequently proposed as a safer alternative for antisepsis in the neonate population as it was, apparently, less well absorbed through intact human skin [78]. Initial research was conducted in rhesus neonates bathed daily for 13 weeks with a skin cleanser solution containing 8% chlorhexidine gluconate (CHG), twice the concentration routinely used at that time [79]. Blood and tissue levels indicated that little systemic absorption had occurred, with only one blood sample having the minimum detectable concentration (11 $ng.mL^{-1}$) at the time. Heel prick and venipuncture were then used to assess the potential systemic exposure to CHG in 34 (28-39 wk GA) newborn infants [80]. While heel prick measurements were all positive, this was explained by residual chlorhexidine in the skin not removed by an alcohol wipe. Venous samples taken 4 h after bathing were 101-460 $ng.mL^{-1}$ in 3 of 7 infants, but only 5% of the samples taken 12 h after the bath were positive. In this study, Hibiscrub (4% CHG in a detergent solution) was used for the daily bath and some of the infants were already a week PNA when the trial began. Further work confirmed the potential absorption of CHD in neonates, particularly in the preterm population, and illustrated the key role of the formulation used [81]. Infants treated with 1% CHD in ethanol had increased plasma levels, whereas the antiseptic was not found in those bathed with 1% CHD and 3% zinc oxide dusting powder. Similarly, when 4% CHG diluted 1:10 was used to bathe full-term infants, no detectable plasma levels (LoD=0.1 µg/mL) were found (although, in this case, the head, a significant surface of a neonate, was not bathed) [82]. In contrast, first- and second-degree chemical burns developed in two twins (26 wk GA) treated with 0.5% CHD in methanol despite the immediate washing of the skin with saline [83]. In fact, alcoholic preparations of CHD are not recommended for neonatal care. Elsewhere, it was reported that 10 of 20 neonates (24-31 wk GA), who were treated with 2% aqueous CHG prior to catheter insertion, had detectable plasma levels (1.6-206 $ng.mL^{-1}$) of the compound, and the highest concentration was observed 2-3 days after exposure [84]. Overall, while the evidence suggests that CHG can be absorbed across the skin of preterm and term infants of less than 2 months of age, the clinical significance of the exposure is unknown [78]. Most of the reported adverse effects are local, such as erythema

and contact dermatitis. Concerning skin burns, the results from different formulations and the effect of alcohol should be clearly discriminated. Other factors determining accumulation are the area of application considered (whole body bath or umbilical cord application) and the exposure frequency. The safety of CHG in preterm infants has been recently reviewed [78] and further investigated [78, 84] given that the FDA has now approved a labelling change which allows the cautious use of CHG products in preterm infants [84].

Propylene glycol (PG) is an excipient commonly found in topical preparations. High plasma and urinary excretion levels have been reported in premature infants primarily from dressings used to treat burns [85]. PG accumulation may result in toxicity such as serum hyper-osmolarity and lactic acidosis [86-87] and, while the parenteral route is typically associated with a larger exposure [88], there have been cases associated with topical application to compromised skin [86]. The WHO has set an acceptable daily limit of PG intake of 25 $mg.kg^{-1}$ for adults [88]. Despite the longer elimination half-life in neonates [87] that could result in greater accumulation, a median PG exposure of 34.1 $mg.kg^{-1}.day^{-1}$ did not affect postnatal renal, metabolic and hepatic adaptation in 60 neonates who were exposed to PG as an excipient as part of their routine therapy [89]. There is little information about the safety of PG in topical and transdermal formulations applied to intact skin.

The undesired systemic absorption of actives formulated for topical treatments is another concern. While exposure to tacrolimus, when given as an ointment to treat atopic dermatitis, is usually low [90], systemic absorption of the drug has been reported for 3 patients (3, 5, and 14 y old) with Netherton syndrome and erythroderma [91]. The systemic absorption of topical steroids used to treat skin diseases has been frequently reported [92-94], and some extreme cases have resulted in depressed adrenal function [93, 95] and development of Cushing syndrome [93, 96]. It is well known that hydrocortisone accumulates in the skin upon topical administration and, interestingly, application of a moisturizer containing propylene glycol to the same skin site caused an increase in plasma cortisol levels, presumably due to mobilisation of drug in the skin 'reservoir' [97].

3.3 Models for paediatric skin absorption

Validated models, with which to predict skin absorption in paediatrics, particularly in the premature and neonatal population, are scarce despite the persuasive evidence that both effective transdermal drug delivery and systemic toxicity following unwanted skin absorption are known to occur in these infants [2, 98-99]. An early compartmental pharmacokinetic model [100] aimed to predict skin absorption in premature infants with no effective SC (Fig 4). The zero-order release rate from a drug delivery system placed directly in contact with the viable epidermis was described by k_0 (mass.area^{-1}.time^{-1}). Drug diffusion across the viable epidermis was characterized by k_2 and the ratio $k_3/(k_0/L.C)$ (where C is the drug concentration in the delivery system of thickness L) acts as a partition coefficient accounting for the relative affinity of the drug between the viable epidermis and the device. This model was used to interpret theophylline plasma levels measured as a function of time in neonates [55]. A series of simulations were also performed to illustrate how changes in the drug's elimination rate constant, the release rate from the device, and its partitioning behaviour affected the pharmacokinetic profile. Key obstacles to extend the approach to other drugs include the estimation of sensible values for k_3 and k_2 in the absence of experimental data and the integration of neonatal developmental and post-natal skin barrier maturation into the model. Indeed, developing a device which adapts drug input to the rapidly evolving skin barrier of the preterm infant represents a significant challenge. In this sense, the vasoconstriction or blanching effect, observed post application of Neosynephrine® to the internal surface of the thigh, has been suggested as a measure of barrier maturity [101]. However, while infants with poor barrier function have been successfully identified with this approach, the test remains qualitative. Further research took the view that the epidermis of preterm infants resembles "*the stripped skin of an adult*" and attempted to develop a model for pre-term skin based on tape-stripped pig ear skin [102-103]. The key advantage of the approach was the quantification of barrier impairment using TEWL (Fig.5). Significantly, the variation of TEWL as a function of the percentage SC thickness retained in the laboratory model and as a function of post-conceptional age (PCA) in neonates *in vivo* was strikingly similar. The correspondence between these profiles therefore allowed barrier maturity to be predicted as a function of PCA: for example, the SC of an infant at 200 d PCA would have only 40% of the mature barrier; by 235 d, the competency would have increased to 75%. Another advantage of the model was its use of readily available porcine skin to investigate and predict skin absorption

in preterm neonates. It was suggested that drug permeability could be characterized for model barriers with different competencies (0-100%) as defined by TEWL, and that validation would require comparison of predicted and previously published data [56]. Subsequently, the permeation of lidocaine hydrochloride, phenobarbital and caffeine was determined across differentially impaired skin barriers, and the steady-state fluxes were fitted to the empirical equation: $J_{ss} = A.e^{(B.TEWL)}$. The value of the constant A was sensitive to the physicochemical properties of the drugs whereas B was similar for all three compounds, suggesting that the level of barrier dysfunction causes comparable, relative effects on the transport of different substances. Despite the significant promise of this approach, little further work has been carried out to develop and validate the model.

A further question concerns variability and the challenge to achieve the appropriate drug input rate in neonates with different levels of skin maturity and different dose requirements. In this regard, the iontophoresis of lidocaine hydrochloride, phenobarbital and ranitidine has been examined [103-105]. The rationale for the approach is that iontophoretic transport is dictated by the relative mobility and concentration of ions present both on both the epidermal and subdermal surfaces of the skin and is less dependent on the inherent skin permeability (Fig. 5). In addition, iontophoretic drug input is easily controllable by manipulating the intensity of current applied [106]. This was nicely illustrated for lidocaine HCl: the cumulative amounts delivered passively across intact and fully compromised skin were 0.7 ± 0.4 and 116 ± 69 $\mu g.cm^{-2}$, respectively, whereas iontophoretic delivery was much more efficient and essentially constant for the two scenarios, 1837 ± 583 and 1979 ± 364 $\mu g.cm^{-2}$ [103]. In the case of phenobarbital, [105] the transdermal flux during iontophoresis increased with skin impairment and the complete removal of the SC lead to a 3.6-fold enhancement relative to intact skin. Interestingly, it was shown that iontophoretic flux remained constant and independent of the skin barrier function, but that passive diffusion, which in this case contributed significantly to the total transdermal flux, increased remarkably as the skin was progressively compromised and eventually overshadowed any benefits from iontophoresis.

4. Paediatric use of transdermal therapeutic systems (TTS).

Scopolamine (hyoscine): Transdermal scopolamine patches (Table 1) aim to prevent the nausea, vertigo and vomiting associated with motion sickness and recovery from anaesthesia. Scopolamine is potent, has a short-half-life and a high incidence of adverse effects directly related to plasma concentration which, combined with its appropriate physico chemical properties, makes the drug a good candidate for transdermal drug delivery. The scopolamine TTS aimed to provide a longer duration of therapy and to avoid peak and trough concentrations associated with side effects and lack of protection, respectively [107]. On the other hand, relative to oral administration, scopolamine patches must be applied 5-6 h before travelling due to slow drug absorption. Scopolamine patches are considered effective to reduce post-operative nausea and vomiting (PONV) in adults but a systematic review of this area excluded children [108]. While transdermal scopolamine has been shown in reducing the incidence of PONV in children, the effectiveness is variable; possibly because of the different timing of patch application relative to the time of surgery [109]. Transdermal scopolamine has also been assessed for the management of sialorrhea in children with developmental delays [110-111]. The labelling of scopolamine patches for the treatment of motion sickness in children is inconsistent: Scopoderm TTS is approved for children over 10 years whereas the label information of Transderm Scop and Transderm-V* (essentially the same patch) precludes their use in children.

The APhA Paediatric and Neonatal Dosage Handbook (P&NDH) [60] suggests the use of scopolamine patches for motion sickness in children older than 13 years; the BNFC [59] also describes two unlicensed indications: the treatment of excessive respiratory secretions, and of the hyper-salivation associated with clozapine therapy. A significant amount of scopolamine in urine was found more than 2 days after patch removal in a study involving hospitalized (3-18 y) children; this observation suggests the formation of a skin reservoir of the drug (although whether this is important is unclear as adverse effects of the drug subsidize quickly upon patch removal) [107]. Paediatric formulations should cater, ideally, for a wide range of doses. In the case of transdermal patches, this is ideally accomplished by using the availability of different sized patches or, in some cases, by cutting an original patch to an appropriate size. The use of transdermal scopolamine patches to treat post-operative emesis in 25 (1-11 y) paediatric patients following strabismus surgery has been described [112]. One quarter of the original patch was used for patients under 2 years, and half a

patch for older patients. In another study, 40 (6-14 y) children wore the uncut, complete patch; and a significant reduction in PONV was observed for the first 48 hours (as well as a greater incidence of dry mouth during the second and third days) [109]. One child suffered hallucinations after the patch had been worn for 36 h that rescinded quickly after patch removal. The BNFC [59] recommends use of a quarter of a patch (1 m-3 y) and half of a patch (3-10 y) for younger children (see Table 1), aiming to reduce the excessive anticholinergic side-effects as described above. However, caution should be taken when cutting patches. For example, some of the visual disturbances observed upon transdermal therapy have been attributed to the contamination of fingers (and subsequent transfer to the eye by rubbing) with the drug through contact with the peeling layer [107]. Another case involved a 14 y patient who removed his patch because of pruritus, and then rubbed his eye [113]. Therefore, careful advice should be given to patients and carers to avoid these unpleasant outcomes.

Fentanyl: Fentanyl patches (Table 1) are licenced to treat moderate to severe persistent chronic pain in opioid tolerant children $\geq$2 y. Although not recommended, the BNFC describes their possible use to treat severe chronic pain in "non-currently treated" 16-18 y old children. Patient-controlled anaesthesia is not considered suitable for younger children so transdermal patches provide a convenient alternative to nurse-controlled or continuous IV administration; further, the youngest children may find it difficult to retain in place buccal and sublingual formulations and swallow them resulting in considerable variability due to subsequent and substantial first pass effect [114-116]. Based on adult data, and particularly the incidence of respiratory depression in post-operative patients, it is sensible to avoid the use of the fentanyl patches for post-operative pain in children. In the case of palliative care, transdermal administration is convenient and minimally invasive for patients with difficulties in swallowing and/or unacceptable morphine side-effects [116-117]. It should be noted that, because percutaneous absorption is invariably slow, passive patches cannot provide acute pain control. To address this limitation, the iontophoretic system, IONSYS^{TM}, was developed although it was not recommended for patients under 18y and the labelling indicated that paediatric subjects might be more prone to skin local effects [118]. There are several generic and therapeutically equivalent fentanyl patches of reservoir and matrix types. The Duragesic patch, originally developed by Alza Corporation, had a reservoir of

fentanyl base in alcohol gelled with hydroxyethyl cellulose and a rate-limiting membrane which provided a drug input rate of 2.5 $\mu g.h^{-1}.cm^{-2}$; different patch areas (10-40 cm^2) allowed delivery from 25 to 100 $\mu g.h^{-1}$. The current Duragesic is a matrix drug-in-adhesive patch and is also available in a size that permits delivery at 12.5 $\mu g.h^{-1}$. This system is of interest since the delivery rate provides an equivalent dose to the 20-40 $mg.day^{-1}$ of morphine frequently used in paediatric cancer pain control [116, 119]. It should be pointed out that a significant amount of fentanyl remains in the patch after use, and that the careful disposal of used systems is essential given their potential for abuse and accidental exposure.

The pharmacokinetics of transdermal fentanyl in children and adults are quite similar [114, 120]. The terminal half-life after patch removal has been reported to be 14.5 h which suggests that a skin reservoir of the drug has built up during the application period [114]. Because fentanyl pharmacokinetics are very variable, a wide range of concentrations are observed after transdermal administration (Fig. 6); nonetheless, the patch avoids the uncertainty and risks associated with the well-known (and, also very variable) hepatic first-pass effect. In 41 (2-18 y) children requiring opioid therapy, transdermal fentanyl was effective and acceptable; the median dose at 15 days was 1.9 $\mu g.h^{-1}.cm^{-2}$ rising to 3.2 $\mu g.h^{-1}.cm^{-2}$ to provide for the rapidly increasing pain experienced by patients with terminal cancer [117, 121]. Younger (<10 y) children required higher weight-normalized doses than older children, an observation in agreement with previous work which found that transdermal clearance in children with cancer was inversely related to body weight [120]. In addition, a higher weight-normalized volume of distribution has been found for neonates and infants [119]. Subsequently, it was confirmed that the patch was useful and well-tolerated in 199 (2-16 y) patients with severe pain and validated the recommendations to convert from oral therapy; in this study, the initial daily dose was 0.98 ± 0.057 $\mu g.h^{-1}.kg^{-1}$, increasing to 1.20 ± 0.09 $\mu g.h^{-1}.kg^{-1}$ over the first 15 days [122]. Use of the new, 12.5 $\mu g.h^{-1}$ patch has resulted in smaller increases in dose requirements, perhaps because this system is intended for earlier stages of treatment. A comprehensive review on the use of fentanyl patches, including pharmacokinetic considerations is available [119].

Most of the side effects reported after transdermal fentanyl have been due to the drug itself. However, adhesion problems (usually solved by additional application of medical tape) and pain on removal due to excessive adhesion have been reported [116-117, 119-

120]. Adhesion may be reduced by movement, skin condition (oily skin), sweating, and behaviour (picking the patch). The skin should be clean and dry before application, and the use of soaps, heat sources, lotions, oils and alcohol -based formulations at the skin site should be avoided. The labelling provides extensive information to patients and carers with comprehensive advice on the correct use and disposal of patches; this is crucial given the high potency of the drug and its potential toxicity [118, 123].

Clonidine: Catapress-TTS® is a reservoir patch that provides continuous delivery of clonidine for 7 days (Table 1). The label information (revised 0ct 2011) indicates that safety and efficacy in paediatric patients have not been established in adequate and well-controlled trials [118]. It is not listed in the BNFC, but the 19th Edition of the APhA P&NDH [60] indicates that children can be switched to transdermal clonidine once an optimal and stable oral dose has been titrated for the treatment of ADHD, hypertension and neuropathic pain [60, 121]. The perceived advantages of the patch are the attainment of consistent levels of drug and the potential for increased compliance [121, 124-125]. As with many other patches, a significant amount of drug remains in the patch at the end of the application period and this has caused toxicity due to inadequate disposal or to unintended transfer of the active [126]. Interestingly, rebound hypertension has not been a problem when patches have fallen off and it is believed that the clonidine skin depot becomes a self-tapering source [124]. The plasma concentration achieved with a given patch depends on the individual renal clearance; usually, steady state concentrations are achieved after 4 days and changes in behaviour begin after 2-3 days [124]. However, it takes about two weeks to see effects other than non-specific sedation and about a month to produce a significant clinical response.

Children are usually started on oral clonidine and then switched to an approximately equivalent transdermal dose [124]. The prophylactic use of transdermal clonidine in 10 (2-8.7 y) children to prevent the withdrawal syndrome commonly observed after several days of deep sedation has been investigated [127]. A transdermal clonidine patch (50-100 μg.day^{-1}) was applied 12 hours before discontinuation of sedative infusions and elective extubation and remained on the skin for 7 days. None of the 8 sedative-tolerant, high-risk patients experienced significant withdrawal symptoms, in comparison to 2 patients who did not received clonidine. Despite of the small numbers of patients studied, clonidine appeared to

be effective for this application. The patch used in this work was not identified but it seems likely (given the delivery rates) that it was cut to provide doses appropriate for different patients. It has been suggested [124], that patches can be cut to individualize doses, although this is strongly discouraged by the APhA P&NDH [60] which recommends the alternative and safer method of simply blocking the unrequired area of the patch with adhesive bandage to limit drug absorption. An 11 y old with hypertension and chronic intestinal pseudo-obstruction (and therefore unable to take oral medication) was treated with the transdermal clonidine and IV enalaprilat to successfully control blood pressure [128].

Transdermal clonidine administration is also associated with adverse skin reactions such as contact dermatitis, erythema and pruritus. These side-effects have been observed as much as in ~40% of the children wearing the patch and develop within 2-3 wk [121, 124-125, 129]. Local dermatitis appears to be worse when a protective cover to ensure adhesion is applied, and the use of a topical steroid cream (e.g., hydrocortisone) has been proposed to alleviate skin irritation [125]. Two toxicity cases in children wearing clonidine patches address the importance of patient and healthcare education on the appropriate use of transdermal patches [125]. In one, a 15 y old with ADHD received an overdose of clonidine when his mother accidentally peeled off the rate control membrane of the patch, in the other, a 6 y old with ADHD developed urticaria under the patch and the resulting scratching may have damaged both the patch membrane and the skin leading to enhanced skin absorption.

Methylphenidate: The prevalence of ADHD is as high as 5-10% in children and 2.4-5% in adolescents [130-132]. Monotherapy with amphetamines or with methylphenidate (MPH) is the first-line pharmacological treatment of ADHD [130]. The Daytrana® patch (Table 1), the first transdermal system developed specifically for the paediatric population, contains methylphenidate (MPH) and was initially approved by the FDA to treat ADHD in (6-12y) children in 2006 and in (13-17y) adolescents in 2010. The patch is not listed in the BNFC and has not been submitted for approval to the EMA [133]. Daytrana®, developed by Noven Pharmaceuticals, is a matrix type patch which uses DOT Matrix™ technology. The drug is solubilized in acrylic adhesive and then mixed with a silicone pressure sensitive adhesive; this forms evenly dispersed pockets of concentrated drug but retains the adhesive properties of the silicone [131, 134]. The product sales and share of the ADHD market were

$64.2 million and 2.1% in 2007 and $78.7 million and 1.8% in 2008 [135]. The short half-life of MPH means that multiple oral doses are required each day; while oral extended release formulations are available, they do not always provide adequate treatment for a complete school day. The patch meets a recommendation that treatment should be extended beyond school hours and also caters for patients with swallowing difficulties [132, 134]. Thus, the transdermal patch allows once-daily administration and avoids the drug's substantial first-pass effect (F_{oral} is 25% and 1%, respectively, for the d- and l-enantiomers). Treatment is usually started with a 10 mg (12.5 cm^2) patch worn for 9 hours; the dose can be increased by 5-10 $mg.week^{-1}$ up to a maximum of 30 $mg.day^{-1}$ (37.5 cm^2 patch) [136]. MPH optimized doses appear to be lower when patients are also enrolled in behavioural treatment [132].

Several studies have characterized the pharmacokinetics, efficacy and safety of the MPH patch in paediatrics (Table 2) [131, 134-137]; an extensive review summarizes pre-clinical, clinical and post-marketing studies as well as the data on efficacy and tolerability [132]. Briefly, the linearity of C_{max} and AUC for patches of different sizes has been shown; it takes ~7-9 h to reach C_{max} although the onset of effects can be observed after 2 hours [131]. MPH is a racemic compound and the d-enantiomer is more active; the total clearance is 0.4 and 0.73 $L.h^{-1}.kg^{-1}$, respectively, for the d- and l- enantiomers; consequently, the systemic levels of l-MPH are ~60-73% of those of d-MPH [131]. The terminal half-life upon patch removal is ~3 h for d-MPH and 1.5h for l-MPH. Because both clearance and first-pass effect are stereo selective, the d/l enantiomer ratio differs after oral and transdermal administration [132, 136]. Typically, very low levels (if any) of l-MPH are detectable after oral administration [130, 132, 136]; in contrast, they are significantly higher (x50 fold) after transdermal delivery even though this enantiomer contributes only ~5-10% of the drug's pharmacological activity. Application of the patch to an inflamed skin site reduced the d-MPH lag time to less than one hour, t_{max} to only 4 h, and caused a 3-fold increase in C_{max} and AUC [131]. The C_{max} of d-MPH was ~50% lower in 13-17 y old children than in those aged 6-12 y; it is unclear whether this is due in any way to skin absorption differences given that changes in bodyweight significantly impacts the pharmacokinetics of MPH after oral medication [132]. The pharmacokinetics of MPH after single and multiple doses of the transdermal patch and of an oral OROS formulation have been compared in children (6-12 y) and adolescents (13-17 y) groups [137]. In agreement with previous results, plasma concentrations were higher

for the younger cohort, and d-MPH accumulation at steady-state was low (although greater by 1.4-1.6 fold for the transdermal group). As expected, l-MPH plasma concentrations were approximately half of those of d-MPH after transdermal administration and negligible after oral OROS.

Overall, MPH patches are well-tolerated by the majority (>75%) of patients [132]. Cutaneous reactions to the MPH patch have been reviewed and their management discussed [138]. Briefly, most cutaneous reactions reported during clinical trials have been mild to moderate. No or only mild discomfort was reported by 73% of patients while 23% experienced moderate but tolerable discomfort and just 2-3% found the patch severely intolerable. There is a low incidence of allergic contact dermatitis when the patch is worn as prescribed (9 h), and allergic contact urticaria is also a rare event. On the other hand, mild to moderate erythema is common. The 12 month tolerability of the patch was investigated in a Phase 3 study in 327 (6 to 12y) children [139]. Application site reactions accounted for 6.7% of study discontinuations and generally consisted of mild erythema associated with mild discomfort at the patch site; all other adverse effects were characteristic of the drug itself and where not associated with the route of administration. Of the 22 who discontinued, 15 were subsequently treated with oral MPH without evidence of systemic sensitization. Dermal adverse effects included rash (n=6) urticaria (n=6), contact dermatitis (n=2), allergic dermatitis (n=2), generalized pruritus (n=2) and skin hyperpigmentation (n=2). The patch adhesion scores after 9 hours of wear were mostly (>96%) “essentially no lifting of patch from the skin” or “lifting of some patch edges”. Nevertheless, following additional studies, the FDA has added a warning to the Daytrana® label regarding contact sensitization as one subject (0.3%) was confirmed to be sensitized to MPH [132]. On a positive note, there was no increase in stimulant abuse following the introduction of the patch to the market [132], perhaps because MPH extraction from the transdermal system is more. A voluntary withdrawal of a limited number of patches took place in 2006-7 as it was reported that parents and caregivers had difficulty removing the release liner [132].

Another placebo-controlled, double blinded investigation evaluated the effect of shortening the wear time of the patch in 128 children (6-12 y) after they had been stabilized on an optimal dose for 5 weeks [140]. On designated days, the children wore an active patch for either 4 or 6 hours and onset of drug activity was observed at 2 hours post- application with

the PERMP (permanent product measure of performance) scores being significantly different to placebo. The scores decreased, consistent with the short half-life of the drug, upon removal of the patch. These results suggest that the transdermal patch can provide additional dosing flexibility, in that its premature removal facilitates a shorter response or more quickly mitigates any signs of side-effects.

Transdermal MPH is not approved for children younger than 6 y although Daytrana® has been used in three preschool children (47-67 m) who had not responded well to other treatments [141]. In the absence of dose guidance for this age group, a slow titration process was followed: Initially the smallest patch (12.5 cm^2) was applied for 1 hour daily; the wear time was subsequently increased by 1 hour every 2-3 days, up to 9 hours by the 4^{th} or 7^{th} week. Depending on response and tolerance, the next size patch (18.75 cm^2) was then adopted and worn for 9 hours. Overall, the three children tolerated a maximum daily dose of 8-15 mg and their condition improved. Adverse effects included mild erythema as well as those associated with the administration of stimulants to pre-school children.

Daytrana® should normally be worn on the hip for 9 hours. Application to the hip and to the scapular area for 16 hours have been compared, and inequivalence between the two sites was found; MPH absorption from the scapular area resulted in lower plasma concentrations and a smaller AUC; bioavailability was ~31% greater at the hip where patch adhesion was slightly better [138]. Once again, parents, carers and patient education about the application site and timing, the length of wear, the use of cosmetics and soap, patch removal and storing are crucial for safe and effective therapy [133, 136].

Buprenorphine: The label information for the Butrans® and Transtec® patches (Table 1) indicates that their safety and efficacy in patients under 18 y have not been established [118, 123]. The APha [60] lists the transdermal buprenorphine patches as one of several formulations to treat moderate to severe pain and opioid dependence but does not provide advice concerning the paediatric use of these patches. Their unlicensed used is listed in the BNFC. While the use of buprenorphine in paediatrics has been reviewed, information concerning transdermal delivery is limited to case reports on pain treatment (but not neonatal opioid abstinence syndrome) [142]. The patch delivering the smallest rate (see Table 1) has been considered more appropriate for paediatrics. When BuTrans® was used to

treat pain in 4 children (3-10 y) with chronic pseudo obstruction syndrome pain control was achieved using 5-10 $\mu g.h^{-1}$ patches in combination with either a fentanyl nasal spray or sublingual buprenorphine for breakthrough pain [143]. Local skin reactions, mild pruritus to erythema, in 3 of 4 patients were treated with a topical steroid spray and, in one case, the application time was reduced to 4 days. It was recommended that re-use of a skin site be avoided for up to 4 weeks. In 16 (2-17 y) paediatric patients with cancer related pain, buprenorphine patches applied to the chest, back or upper arm, and changed every 3 days, were useful and well-tolerated. The dose rate was titrated from 8.75; 17.5; 35; 52.5; 70 to a maximum 140 $\mu g.h^{-1}$. The smallest inputs were obtained by cutting the 35 $\mu g.h^{-1}$ patch into 2 or 4 pieces to provide either ½ or ¼ of the delivery. After 2 weeks, ~70% of the patients had responded to transdermal buprenorphine although some required rescue medication; the mean dose was 32.6±14.8 $\mu g.h^{-1}$ and the range 8.75-70 $\mu g.h^{-1}$ [144].

Tulobuterol: The tulobuterol patch (Table 1), commercialized as Hokunalin® Tape in Japan and Korea, and as AmiaidR in China, aims to improve the respiratory distress associated with airway obstruction in bronchial asthma, acute bronchitis, chronic bronchitis and emphysema. The label indicates its use for 6 m or older children. This potent bronchodilator was extensively used in oral formulations, but the patch was developed to alleviate the so-called “morning dip”, or decrease of respiratory function, experienced upon waking by many asthma patients. The matrix type patch contains both crystallized and molecular forms of the drug in an adhesive layer; the solid drug provides a reservoir to maintain the sustained and continuous delivery of the drug [145]. The drug plasma concentration peaks 8-12 hours after patch application in adults; hence, a patch applied at bed-time is able to control early morning symptoms [146]. The patch is also suitable for children who have difficulties in taking oral tablets. The pharmacokinetics of tulobuterol after transdermal administration have been assessed in 6 boys (4-13 y) with previously controlled moderate to severe asthma but admitted to hospital following a severe, acute, attack [146]. The patch, containing 0.2 $mg.cm^{-2}$, was applied to the chest for 24 hours. The doses were 1 mg (<30 kg) and 2 mg (≥30 kg) depending on body weight. Plasma levels started to increase 4 h after application and C_{max} was attained at 12 hours (Fig.7); drug concentrations decreased gradually after patch removal. The peak expiratory flow rate significantly increased after application and was significantly higher than control 22 h after patch application; this result further supports the

hypothesis that a patch applied at bed time would prevent the “morning dip” efficiently. No side effects were reported.

Oestrogen therapy: Treatment with oestrogens may be required for the development of female secondary sexual characteristics. According to the BNCF [59], puberty can be induced with increasing doses of ethinylestradiol and as guided by breast staging and uterine scans; cyclical progestogen replacement is added after 12–18 months of oestrogen treatment. Once the adult dosage of oestrogen has been reached, a low-dose, oral oestrogen-containing contraceptive is advised. Nevertheless, most of these treatments are unlicensed and the use of transdermal patches is not specifically described (Table 1). The AphA 19th Ed. [60] indicates the use of transdermal estradiol patches such as Climara®, Alora®, Estraderm®, Menostar® and Vivelle Dot® to treat female hypogonadism. While the label information of some of the patches includes their possible use to induce puberty, and indicates the risks associated with large and repeated doses of estrogen over a long period, there is no information specified about their efficacy and safety in children [118].

Traditionally, the induction of pubertal development in girls had been managed with oral estrogens. While effective, this therapy has disadvantages, such as variable bioavailability due to intestinal and hepatic first-pass effects as well as changes in liver activity and blood clotting [147]. Further, the treatment has to be delayed with respect to the age of spontaneous puberty to avoid a negative impact on the patient’s final height, often resulting in some psychological sequelae [147]. Key advantages of the transdermal approach is avoidance of pre-systemic first-pass effects and the availability of matrix patches, which can be cut into smaller systems to pieces allow puberty induction to be started earlier using very low doses [147-149]. A clinical study in 15 girls with hyper- or hypo gonadotropic hypogonadism were treated with transdermal estradiol (Evorel® 25µg.day^{-1}) [147]. Pubertal induction was started for 12.3-18.1 y patients using a quarter of the patch (6.2 µg.day^{-1}) applied to the buttock at night-time; the dose was reduced to 4.2 µg.day^{-1} in some patients with high (>40 pmol.L^{-1}) serum estradiol. The initial dose was maintained for 4-14 months to mimic hormone levels in early puberty and to prompt breast development to stage 2. Subsequently, the dose was increased to attain mid-puberty levels and development to breast stage 3. Progestogen was added to the estradiol treatment within 2 years of induction. The results indicated that the procedure allowed the spontaneous levels and

diurnal variation of serum 17-β-estradiol in early puberty to be achieved, but that further refinement would be required to mimic levels in mid puberty. Breast development (corresponding to breast stage 2) occurred in 12 of the 15 girls within 3-6 months of the first patch application.

Ovarian failure affects ~90% of females with Turner syndrome (TS) and requires hormone replacement therapy [149]. A one year study in 12 (14.0 ±1.7 y) girls with TS compared oral versus transdermal estrogen (Vivelle TD system) treatment for pubertal induction [149]. The transdermal group was treated with a 25 μg patch twice a week for 6 months, followed by a 37.5 μg patch twice a week for the second 6 months. The oral oestrogen dose was 0.3 $mg.day^{-1}$ every day for the first 6 months, followed by alternating 0.3 mg and 0.625 mg daily doses for the next 6 months. The transdermal treatment resulted in a greater change in spine bone density (bone mineral density and content) and greater increases in uterine length and volume. No differences were found in other parameters such as IGF-1 and lipid profile, or growth velocity and body composition. At the end all bar two girls, one in each arm of the study, had progressed to Tanner stage III-IV.

A 2011 investigation on 128 (13.5±0.5 y) girls with Turner syndrome revealed a significant increase in the use of transdermal oestrogen over the preceding 4 years reflecting, presumably, the view that the patches provide a more physiologic and favourable mode of oestrogen replacement [150]. The literature through 2013 comparing oral versus transdermal exogenous pubertal induction has been reviewed, and dose equivalences between the two therapeutic approaches has been pondered [148]. Although transdermal therapy seems promising, there is clearly a need for large-scale, multicenter studies to properly validate the positive results from the limited (in terms of patient numbers) assessments performed to date.

Nicotine: The numerous nicotine transdermal systems available in the market (Table 1) aim to treat nicotine withdrawal symptoms (NRT). According to the FDA labels [118] medical advice should be sought for individual younger than 18 y. In the EU, several nicotine patches are authorized for the 12-18 y old population although, due to the lack of information concerning this age group, medical advice is recommended after 3 weeks of treatment [123]. In 2009, in England, 52% of 15 y olds had tried smoking and 15% were regular

smokers. Providing help to adolescents to quit successfully is a public health target because most regular smokers start during adolescence. As a result, NRT formulations were made available to all 12-17 y old in 2005 in the UK [151]. An analysis of the changes in NRT prescribing between 2005 and 2009 revealed that it was highest for 16-17 y olds and lowest for the 12-13 y age group (less than 10 prescriptions per 100,000 adolescents per month) [151]. It was concluded that the recent licensing modifications in the UK had little effect on prescribing practice. A later, self-reporting study from the USA found that 5% (n= 4078) of 11th graders (16-17 y) reported current or former NRT use; the exclusive use of gum (42%) was twice as likely as the exclusive use of a patch (29%) [152].

Attempts to quit, typically motivated by concern about current and future health, are common among young smokers [153]. However, the efficacy of NRT in adolescents is considered to be lower than in adults (although it has been successful in some trials involving highly addicted (>10 cigarettes.d^{-1}) participants with substantial comorbidity [153]). A 2011 meta-analysis found that NRT for smoking cessation in adolescents had no significant effect on abstinence rates at short and mid-term follow-up (<26 weeks) [154]. It was also pointed out that most trials have involved a limited number of participants and that low compliance may be contributing factor. Few adverse effects, mostly itching (33-62%) and redness (15-52%), have been reported when using nicotine patches [154]. A double-blind, placebo controlled trial of a nicotine patch involved 100 (13-19 y) subjects, who had smoked at least 10 cigarettes per day in the last 6 months, did not use any other tobacco product more than once a week, were motivated to quit smoking, and were not on any other NRT product [155]. The most common adverse effects (but not considered serious) were itching and redness at the skin site, sleep problems and abnormal dreams, joint, muscle and stomach aches, and light-headedness. Participants using the nicotine patch reported fewer withdrawal symptoms, including craving, and while it was concluded that the patch might be a promising medication, further trials were considered necessary.

The use of transdermal nicotine to complement the effects of haloperidol in the treatment of Tourette's syndrome has also been proposed [156]; the first trials involved nicotine gum but, despite beneficial effects, patient compliance was limited by the bitter taste and by gastrointestinal effects. Results from the mostly uncontrolled studies have been summarized [156].

Other actives: The use of transdermal selegiline (EMSAM) in paediatrics has been investigated [157]. However, because of concerns about the use of antidepressants in children and adolescents, and an increased risk of suicide, the patch is not approved for paediatric use [118]. Concerning the contraceptive patch, ORTHO EVRA® (norelgestromin/ethinyl estradiol), the label indicates that safety and efficacy have been established in women of reproductive age, i.e., both for post-pubertal adolescents under 16 y and for those 16 and older [118, 158]. For EVRA patch, (which delivers oestrogen at a greater rate) the label information indicates that its use and efficacy has been established only for women > 18y [123].

5. Innovative methods for paediatric transdermal drug delivery.

The latest advances and state-of-the-art in methods to enhance transdermal delivery, and therefore expand the number of drugs deliverable by this route of administration, have been recently reviewed [6]. Enhancement methods are broadly classified into non-invasive approaches that maintain the integrity of the SC and minimally invasive strategies that disrupt the SC barrier.

Iontophoresis uses a small electrical current (<0.5 $mA.cm^{-2}$) to enhance molecular transport across the skin and can be used for drug delivery and non-invasive sampling applications [106]. This technique is probably the most established among the non-invasive methods, which apply a source of energy to enhance skin permeation. Indeed several iontophoretic devices have been approved and marketed [106]. The earliest paediatric application was the iontophoretic delivery of lidocaine to provide local anaesthesia prior to venous sampling and minor dermatological interventions. Implementation first involved the use of a power supply (Iomed® Phoresor II Auto) and disposable electrodes, which could be either filled prior to use by the practitioner [159] or prefilled (NumbyStuff®) [160] with a solution containing 2% lidocaine and 1:100,000 epinephrine. The second active aimed to induce local vasoconstriction and reduce lidocaine clearance into the systemic circulation. Compared to the conventional EMLA cream (2.5% lidocaine and 2.5% prilocaine) iontophoresis provided a faster onset of anaesthesia and, sometimes, in children, a greater depth of dermal penetration [160-161]. The efficacy of iontophoresis versus placebo in children has been demonstrated [159, 162]. In 13 patients, 11-19 y, iontophoresis was compared with

subcutaneous injection, which was more painful but more effective; similar levels of anxiety were generated by both methods [163]. While the preponderance of evidence suggests that iontophoresis is a safe and effective method, there is disagreement about the level of paediatric satisfaction; this is probably related to the different iontophoretic procedures followed and to the age of the patients involved. Some practitioners have found iontophoresis a complicated method as compared to EMLA cream application.

A significant improvement, therefore, was the development of the LidoSite® device by Vyteris, Inc. (Fair Lawn, NJ) that was approved by the FDA in 2005 (although it is no longer commercialized). The system comprised (a) the single-use, disposable LidoSite® Patch which contained a 5 cm^2 drug reservoir, and (b) the LidoSite Controller, a portable, microprocessor-controlled, battery-powered DC current source sufficient for up to 99 drug (1.77 mA-10 min) applications. This iontophoretic lidocaine delivery system was small, easy to use and pre-programmed, therefore minimizing variability in the dose and rate of anaesthetic administration. A study in 12 healthy children found that the system was well tolerated. An optimized formulation (10% lidocaine and 0.1% epinephrine) was used and provided anaesthesia in only 10 minutes; systemic exposure to lidocaine was very low with 11 out of 12 subjects showing concentrations below the LoD (5 $ng.mL^{-1}$), and the other slightly more (8.9 ng.mL mL^{-1}) [164]. Quite likely, the increased content of lidocaine (compared to previous formulations) resulted in a larger drug transport number (and iontophoretic flux) [165]. The reduced epinephrine content was selected to achieve a degree of vasoconstriction so that the local anaesthetic residence time was adjusted appropriately without compromising the venipuncture procedure. The effectiveness of the iontophoretic delivery of a lidocaine/epinephrine for the provision of tympanic membrane anaesthesia to treat acute, chronic and recurrent otitis media was the object of a non-randomized, multicentre, prospective, clinical study sponsored by Acclarent which involved 12 months and older children according to the data base ClinicalTrials.gov. [166]; unfortunately, no results have yet been posted.

The iontophoresis of dexamethasone phosphate, a common procedure in physiotherapy, was recently tested for the treatment of temporomandibular joint involvement in juvenile idiopathic arthritis (JIA) as a less invasive alternative to intra-articular steroid injections [167]. The study involved 28 (2-21 y) JIA patients, most of whom completed the 8-10

iontophoresis sessions. Approximately 2/3 of the subjects experienced an improvement or a normalization of the temporomandibular joint range of motion and the associated pain [167]. While this small study suggests that dexamethasone iontophoresis is safe and effective, further studies are required to determine the optimum dosing and to compare iontophoresis with intra-articular steroid injections. Iontophoresis has been suggested as an approach to deliver other actives such as methylphenidate [168], ranitidine [104] and phenobarbital [105]. While these investigations have sometimes suggested the feasibility of delivering therapeutic doses, at least for some age groups, only *in vitro* studies have so far been carried out (Fig.5).

Iontophoresis can also be used to non-invasively sample drugs and clinical markers. The Glucowatch Biographer® (developed by Cygnus, Inc.), which was able to monitor blood sugar over the entire range of glycaemia, received a CE Mark for children (7-17 y) in 2000 and FDA paediatric (7-17 y) approval in 2002. This device provided the first truly non-invasive approach to the monitoring of blood glucose and was considered accurate and safe [169]. However, use of the device provoked some irritation (itching, swelling, mild to strong erythema) which obliged application sites determined to be rotated, a perceived limitation in smaller patients. An interesting feature was the “down alarm” which signalled a 25% fall in the blood glucose concentration and a possible, impending hypoglycaemia, which might then be prevented. However, it was later reported that the decreased accuracy of the Glucowatch Biographer® at lower glucose levels meant that the alarm setting required to detect a high proportion of hypoglycaemic events would result in a high number of false alarms [170]. Regrettably, the commercialization of the device was suspended in July 2007 and the Glucowatch Biographer® is no longer available. Subsequently, and primarily in adults, iontophoresis has been used to sample phenyl-alanine (phenylketonuria) and markers of renal disease such as urea and iohexol [106]. A small pilot study in paediatric patients suggested the possibility of assessing glomerular filtration rate via the iontophoretic extraction of iohexol [171].

Other innovative, passive patch technologies have appeared. The S-Caine Patch™ (ZARS Inc.) (Table 1) includes a drug reservoir containing a 1:1 eutectic mixture of lidocaine and tetracaine and excipients (polyvinyl alcohol, sorbitan monopalmitate, water, methylparaben and propylparaben) (Fig. 8). The CHADD, controlled heat-aided drug delivery system,

comprises iron power, activated carbon, sodium chloride, wood flour, water and filter paper [172]. Upon removal from the protective pouch and exposure to atmospheric oxygen, an exothermic reaction occurs causing the patch heat up and increasing skin temperature by ~5°C [173]. The effectiveness of the heat-aided patches was first demonstrated in adults [174], and the device was commercialized as Synera™ (USA) or Rapydan™ (Europe) and approved for paediatric use [175]. The surface area of the patch is 50 cm^2 but drug is delivered through only 10 cm^2. According to label information, safety and efficacy have been established in paediatric patients 3 years and older in well-controlled studies, whereas only safety has been demonstrated in a clinical study involving 34 children of 4-6 months [118]. In an investigation with 64 (3-17 y old) children, either the S-Caine Patch™, or a placebo (including the CHADD component) was applied for 20 minutes prior to venous access. The S-Caine Patch™ considerably reduced pain compared to placebo; a 100% success of vein entry and cannulation was reported for both groups, partially explained, at least, by a heat-induced vasodilatation effect. In 40 (3-17 y) patients, who required IV catheter access, the Synera™ patch (mean application 39 min) was evaluated against an identical placebo (mean application 33 min) that also contained the CHADD element [176]. Ease of cannulation was similar for both groups but more subjects using the Synera™ patch reported adequate anaesthesia. EMLA and Rapydan™ patches were compared in 200 (3-13 y) children [177]. The application time was 35 minutes in both cases; visibility of veins and success of a venipuncture procedure were the same for both groups, while erythema was more frequent for the Rapydan™ treated children, who also experienced less pain. The latter outcome was not unexpected, however, as the EMLA patch should be applied for at least 1 hour before the intervention. The systemic exposure to lidocaine and tetracaine depends on the number of Synera™ (or Rapydan™) patches worn and the duration of the application. For example, the simultaneous application of two patches for 60 minutes resulted in plasma lidocaine concentrations of 16.8 $ng.mL^{-1}$ and 2.1 $ng.mL^{-1}$ in children aged 3-6 y and 7-12 y, respectively; tetracaine was < 0.9 $ng.mL^{-1}$ for all age groups [173]. The EMLA system (Table 1) is available in Australia, France and Canada, and is essentially a patch version of EMLA cream that aims to provide easier use and more precise therapy [60, 178]. While the EMLA patch can be applied to younger children (under 3 months but not newborns) it must be applied for at least an hour to achieve adequate local anaesthesia. Nevertheless, the efficacy of the EMLA patch in the paediatric population has been reported

[178-184]. The LidoDerm® product (700 mg of lidocaine in an adhesive patch of 140 cm^2) (Table 1) is indicated for the treatment of post-herpetic neuralgia in adults and its safety and efficacy has not been established in children; nevertheless this patch was compared with a placebo in 72 paediatric (4-15 y old) patients. It was found to be effective in reducing the pain of venipuncture but not that associated with rocuronium injection [185].

Among the so-called minimally invasive technologies, liquid-jet and powder-jet injectors have been proposed for the delivery of vaccines, insulin, sumatriptan, and human growth hormone. Some of these devices have been commercialized and tested in children [6, 186-188]. In particularly, significant work has been undertaken with respect to the delivery of growth hormone, with several devices (Medi-Jector®, ZomaJet® 2 Vision, SeroJet®, Genotropin® ZipTip, Cool.click™) already tested and commercialized as recently reviewed [188]. However, discomfort and local side-effects may limit their application in children [6, 188]. The Biojector® 2000 is a needle-free system cleared by the FDA to deliver intramuscular injections; it can also deliver subcutaneously and has also been tested for intradermal administration in clinical trials [118]. For example, the ability of the Biojector 2000 to inject intradermally a fractional dose of an inactivated poliovirus vaccine was compared to the intramuscular injection of the full dose in 471 infants at weeks 6, 10 and 14 of age [189]. A greater number of minor local reactions (induration, redness and pain) was observed with the needle-free injector which was the method preferred by parents. However, a lower immunogenicity was observed for the intradermal injection, possibly due to the different doses administered. In another study, 50 children (4-10 y) with diabetes were asked to compare one administration of saline with the needle free device “cool.click” to their morning insulin needle injection [190]. Adverse reactions to the “cool.click” device included minimal bleeding, without hematoma, bruising and skin lacerations. Pain or discomfort was absent in 52%, slight in 40% and severe in 8%; 38% of children had no fear, no worry; 52% had little fear/worry; and 10% were very worried. Overall, the children found the needle-free device easier to use and more comfortable than their insulin needle injection, and 74% preferred it over needles. Another investigational, single-use, disposable powder-jet injector (ALGRX 3268), which delivered powdered lidocaine (0.35 µm particle size) was investigated in 145 (3-18 y) children for its ability to reduce pain before venipuncture [191]. A placebo (empty drug cassette) and injectors delivering 0.25 and 0.5

mg of lidocaine were compared; all three contained helium gas pressurized at 20 bar. The system was effective compared to placebo, and required only 2-3 minutes to provoke anaesthesia, much shorter than the 10-15 minutes and 30-90 min required for iontophoretic and passive formulations, respectively. Patients using the active injector were more likely to develop erythema and petechia. A randomized, double-blind, sham, placebo-controlled, single-dose phase 3 study evaluated the efficacy and safety of an intradermal powder injection device involving 579 (3-18 y) volunteers undergoing venipuncture or cannulation procedures [192]. The device contained 0.5 mg lidocaine hydrochloride monohydrate (40 μm) and medical grade helium (21 ± 1 bar); the sham placebo device was identical except that lidocaine was absent. The active system was described as more effective than the sham placebo. Dermal reactions (erythema, petechia) were "minor, short-lived and self-limited". Again, the greatest benefit of this device was that the analgesic effect occurred within 1-3 minutes after administration. The J-Tip® is an FDA-approved injection for inducing local anaesthesia; in this case, buffered lidocaine is delivered under high pressure from a compressed carbon dioxide gas cartridge, allegedly to a 5-8 mm depth in 0.2 seconds [193]. The system has been compared to EMLA cream in 116 (7-19 y) volunteers and was well tolerated; further, according to the authors, the J-Tip® provided faster anaesthesia than the cream and was cost-effective.

Microneedles (MN), another example of new, rapidly evolving technology, are described as an array of micro-projections, typically from 25 to 2000 μm in height, of a variety of different shapes, and attached to a base support [194-195]. Upon application to the skin surface, the MN open transport pathways of micron dimensions across the SC. Comprehensive reviews on MN including their fabrication, classification, available devices and their applications in drug delivery, including immunization, are available elsewhere [194-196]. MN effectively bypass the SC barrier and therefore expand the applications of transdermal drug delivery to large molecular size entities. Nevertheless, because MN are most suitable for the administration of relatively small doses, they have been primarily targeted to large and potent drugs such as biopharmaceuticals. Although the use of MN to deliver disease modifying antirheumatic drugs in paediatrics is considered to be potentially advantageous, they have been tested in children on only limited occasions [186]. The delivery of desmopressin using a MN array (Macroflux®) to hairless guinea pigs was efficient

and well tolerated, suggesting its potential use to treat enuresis in young children [197]. Two studies [198-199] investigated the delivery of insulin to children and adolescents with type 1 diabetes. The first in 5 subjects compared the delivery of intradermal insulin via a single hollow microneedle with subcutaneous insulin administered via a catheter administration [198]. There were no differences in insulin AUC but absorption was faster for intradermal insulin as indicated by t_{max} (27 ± 13 min and 57 ± 20 min for MN and catheter administration, respectively). The pain associated with inserting the MN was significantly less than that associated with the catheter, but there were no differences in the pain scores related to insulin infusion. There was less erythema associated with MN, but the new administration method resulted in more oedema, described as a "fluid bleb", which was due to displacement of the skin surface by the insulin solution. The second study, in 16 (10-18 y) participants, compared intradermal (MN) and subcutaneous (syringe pump) routes of administration [199]. The hollow microneedle was inserted into the abdomen and this procedure was reported as less painful. The pain scores associated with the insulin infusion were higher for the MN (although the difference was not significant). It was suggested that lowering the flow rate, addition of hyaluronidase, and increasing the MN size to reduce the infusion pressure would improve the acceptability of the approach. Another investigation in 384 (4-66 m) children has evaluated skin thickness (epidermis + dermis) at four different body sites (deltoid, suprascapular, upper back and lumbar area) considered suitable for intradermal vaccine injection [200]. Skin thickness did not depend upon age, gender, BMI, and phototype, but was significantly higher (a) at the suprascapular area (1.30 mm) than the deltoid (1.22 mm), and (b) on the upper back (1.39 mm) than the lumbar area (1.31 mm). However, these differences were considered clinically irrelevant with respect to vaccine delivery meaning that MN of different lengths would not be needed to routinely vaccinate children aged up to 5 years.

Other minimally invasive techniques, such as thermal microporation, are at different stages of development. The effect of laser-ablation of the SC prior to application of a lidocaine cream was investigated using a FDA approved, lightweight and portable Er:YAG unit with a fluence of 3.5 $J.cm^{-2}$ and a spot diameter of 6 mm; the control was a sham laser [201]. The laser exposure time was 600 μs and the cream was applied for 5 minutes. Adults and 15 (3-17 y) children were studied and the procedure was reported to be effective and did not

provoke any persistent erythema or infection. However, any conclusions were limited by the small number of children involved in each age group. Elsewhere, the SonoPrep® (sonophoresis) device was used in 50 (5-10 y) children again to reduce the time required to achieve local anaesthesia following application of EMLA cream [202]. The skin site was treated with either the SonoPrep® or with sham sonophoresis, and the cream then applied for 5 minutes. The SonoPrep® intervention reportedly caused minimal discomfort (with only 2 of 21 children complaining of minor skin reactions) and reduced the pain due to IV cannulation. However, while the pain scores were determined by blinded researchers, the children's parents were not; further, subject numbers were probably too small to detect any rare side-effects of sonophoresis and, finally, the control group received no effective pain relief because a 5-minute EMLA application is insufficient for this purpose. It follows that a more objective study design is required to substantiate the conclusions of this work.

6. Conclusions

TDD has been successfully translated from adults to the paediatric population primarily in the form of patches which, in some cases, were specifically developed for the paediatric population. An important disadvantage of passive patches is the significant amount of drug remaining in the patch upon its removal after use. For example, only 36% of the MPH loading in a Daytrana patch is absorbed during a 9 h application [133]. Obviously, the drug left in the patch provides the opportunity for abuse and accidental exposure [141]. A different risk occurs when a transdermal patch is worn by an adult and inadvertent transfer to children occurs. Other problems occur when, for example, the same patch is applied twice, a patch is applied for too long, or increased skin absorption is caused by use of heating pads [203]. Comprehensive advice must be provided on the correct use and disposal of transdermal patches independent of the age of the patient. The potential for irritant contact dermatitis and allergic contact dermatitis should be considered (but, for most drugs, only mild effects are seen; moderate erythema is the most common skin-effect) [138]. Again, education is crucial to reduce the incidence of contact dermatitis and to respect the site and duration of application [138]. Poor adhesion has also been reported as a limitation with respect to the use of transdermal patches [138,204-205].

Not all the marketed patches are licenced for paediatric use. Some patches are used unlicensed and lack an appropriate range of doses (areas) for paediatric therapy. As a result, health carers frequently cut patches proportionally to the dose reduction required. The practice of cutting patches is routinely discouraged by manufacturers and, in fact, there is little information about the risks (either of over- or under- dosing) involved. There is a general pre-assumption that the risk of toxicity associated with drug leaking from a patch is greater for reservoir patches systems but this may not always be the case (as shown recently for a fentanyl product) [206]. As a corollary, extrapolating a practice established as safe for a given patch (brand or formulation) to another patch containing the same drug without consideration of differences in structure and composition may result in unexpected outcomes.

On the positive side, transdermal patches have improved drug therapy in children. This is a non-invasive route of administration which avoids first-pass effects (oestrogen and ADHD therapy) and provides controlled and prolonged plasma levels. For example, the bed-time application of the tulobuterol patch ensures appropriate plasma levels upon waking the following morning, and the MPH patch sustains drug delivery throughout the school day. Patches are easier to use, especially for patients who experience difficulties in swallowing, and are less disruptive to the daily routine of parents and carers, thereby facilitating adherence. Finally, transdermal patches allow individual dose titration by modification of either the patch size or wear time [135, 140-141].

Significant advances in innovative methods for transdermal drug delivery have been achieved and these methods may be progressively translated to paediatrics as safety and efficacy is established in adults. A specific example is iontophoresis, for which two devices have been approved for paediatric use.

Nevertheless, major challenges remain with respect to the translation of TDD devices and formulations to the premature neonates because of their immature and rapidly evolving skin barrier function. Research is urgently needed in this area to ensure that this vulnerable population enjoy the benefits of this unique, non-invasive route of drug delivery.

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Table 1

Drug	Brands Area/drug content/nominal rate	Labelled and unlicensed uses
Scopolamine (hyoscine)	Scopoderm TTS® Transderm Scop Transderm-V* 2.5 m^2/ 1.5mg/ 1mg over 72 h	*Label:* Scopoderm TTS for prevention of motion sickness in ≥10-18 years *Unlicensed use:* BNFC: Excessive respiratory secretions: 1m-3y: quarter of a patch /72h - 3-10 y: half a patch/72h and 10-18 y:1 patch/72 h BNFC: Hypersalivation associated with clozapine therapy: 10-18y:1 patch/72h APhA: Motion sickness: >12y:1 patch/72h
Fentanyl	Duragesic DTrans®; Duragesic® Fencino®, Fentalis®, Matrifen®, Mezolar®, Osmanil®, Tilofyl®, Victanyl® and several generics Aproximate ranges: 5 to 42 cm^2 2.1 to 16.8 mg 12.5 to 100 µg/h	*Label:* for management of persistent, moderate-to-severe chronic pain in opioid tolerant patients currently receiving opiates in > 2y. *Unlicensed use:* BNFC: severe chronic pain in 16-18y not currently treated with strong opioid analgesic; although warning about serious risks of fatal respiratory depression. *Additional information:* See labelling, BNFC and APhA for several warnings concerning the use of fentanyl and patches.
Clonidine	CatapresTTS®-1; -2; -3 3.5; 7.0 and 10.5cm^2 2.5; 5.0; 7.5mg 0.1; 0.2 and 0.3 mg/day over a week	*Label:* safety and effectiveness not established in paediatrics.- *Unlicensed use:* APhA: Management of hypertension, ADHD and neuropathic pain. Children and adolescents can be switched to transdermal after titration with oral dose. The transdermal dose approximately equivalent to the total oral daily dose may be used. *Additional information:* The patch contains aluminium and must be removed before undergoing MRI
Methylphenidate	Daytrana™ 12.5; 18.75; 28.0; and 37.5 cm^2 27.5; 41.3; 55; 82.5 mg 1.1; 1.6; 2.2; 3.3 mg/h during 9 h	*Label:* FDA approved for treatment of ADHD in 6-17 y *Additional information*: (APhA): Long term use of the patch (and other dosage forms) has not been adequately studied and should be re-evaluated periodically for the individual patient.
Buprenoprhine	BuTrans® 20.25; 30.6; 51.84 cm^2 5, 10, 20mg 5, 10, 20 µg/h for 7 days TransTec 35®; 52.5®; 70® Active area: 25; 37.5; 50 cm^2 20, 30 40 mg 35, 52.5, 70 µg/h for 4 days	*Label:* safety and effectiveness not established for < 18y; not recommended for paediatric use. *Unlicenced:* moderate to severe pain BNFC: Approximate equivalence provided for BuTrans® and TransTec® patches and oral daily doses of morphine. APHa: BuTrans® listed without further advice

Tulobuterol	Hokunalin Tape 2 mg (AmiaidR) 6m-2y 0.5 mg of the tape 3y-8y 1 mg of the tape ≥ 9y 2mg of the tape	*Label:* improve respiratory distress caused by airway obstruction of bronchial asthma, acute bronchitis, chronic bronchitis, or emphysema in ≥ 3 y.
Estradiol	Climara® ; Alora® ; Estraderm ® Vivelle Dot®, Menostar®, and others. 2.5 to 25 cm^2 0.39 to 8 mg 75 to 100 µg/h Once weekly and twice patches	*Label*: safety and effectiveness in paediatric patients not established although some labels indicate their possible use for induction of puberty in adolescents. *Unlabelled:* APhA: Female hypogonadism in adolescents. Use lowest effective dose for shortest duration possible consistent with an individual patient. See APha dosing guidelines for once- and twice weekly patches. *Additional information*: Some of these patches contain aluminium and must be removed before undergoing MRI
Nicotine	NicAssist; Nicotinell TTS; NiQuitin; Habitrol ; Nicoderm ; ProStep and others. Several presentations; range: 5-25 mg/16h or 7-21 mg/24h Examples: Nicotinell TTS 30: 30 cm^2 active area/ 52.5mg / 22 mg/24h NiQuitin 14: 15 cm^2 active area / 78 mg / 14 mg/24h	*Label:* Nicotine replacement therapy > 12y. Some labels indicate seek medical advice after 3 weeks treatment. FDA: Seek medical advice for < 18y, some patches not for sale for <18y *Additional information*: See BNFC and specific product labelling for dosing titration and guidelines.
Lidocaine:tetracaine	Rapydan®/Synera® 50 cm^2 (active 10 cm^2) 70 mg of each active	*Label:* Provide local anaesthesia for superficial venous access and superficial dermatological procedures for children ≥ 3y. Safety demonstrated in 4-6 months *Additional information:* The patch contains iron and must be removed before undergoing MRI
Lidocaine:prilocaine	EMLA® patch 40 cm^2 (active 10 cm^2) 2.5% of each active in each 1g patch.	*Label:* Provide local anaesthesia for minor procedures (IV cannulation or venepuncture, superficial minor surgery in neonates and older. Safety not established in premature infants.
Lidocaine	Lidoderm® and generics 140 cm^2; 700 mg	Not licensed for paediatric use.

Table 1: Details of transdermal patches that have been used in children and their labelled and unlicensed uses. Information gathered from BNFC, APhA 19th Ed, and the Drugs@FDA, and Electronic Medicines Compedium databases [59-60,118, 123].

Table 2

Dose (mg) delivered in 9h	Patch size (cm^{-2})	Nominal delivery rate ($mg.h^{-1}$)	MPH content (mg)	C_{max} ($ng.mL^{-1}$)		AUC_{0-12h} ($ng.h.mL^{-1}$)	
				d-MPH	l-MPH	d-MPH	l-MPH
10	12.5	1.1	27.5	20.0	14.6	145	86.2
15	18.75	1.6	41.3	23.9	15.0	181	100
20	25	2.2	55	30.5	18.4	229	129
30	30	3.3	82.5	46.5	29.5	378	229

Table 2: Characteristics of the methylphenidate transdermal systems (Daytrana®) commercially available to treat ADHD, and mean values of observed pharmacokinetic parameters: C_{max} and AUC_{0-12h}. The lower values of these parameters for the l-enantiomer of MPH are consistent with its higher systemic clearance (see text for details). Data taken from references [118,131].

Figure Captions

Figure 1: Skin blanching (left panel) following a 30 second application of 20 µL of a 1% epinephrine solution and corresponding TEWL measurements (right panel) as a function of postnatal age for infants born at < 30 weeks; 30-32 weeks; 33-36 weeks and ≥ 37weeks of gestational age. The drug solution was applied to the same abdominal site immediately after TEWL was measured. The shaded area indicates the range of TEWL in mature infants. See ref. for complete details. Reprinted from Harpin et al., 1983 [29] with kind permission from Elsevier.

Figure 2: *Top panel: In vitro* phenobarbital flux across skin sourced from 7 preterm and full-term deceased infants as a function of GA at birth; the PNA for each neonate is indicated. The drug delivery system was 39 $\mu L.cm^{-2}$ of a 2 $mg.mL^{-1}$ phenobarbital solution in ethanol. Post-application, the solvent was allowed to evaporate and the experiment was run for 12h. The dotted lines indicate the corresponding flux (mean ± SD) for adult skin. *Bottom panel:* Diamorphine permeability coefficient (K_p) across neonatal cadaver skin as a function of the GA at birth; PNA age was 1-3 days unless specified otherwise. The donor formulation was 3.4 mL of a 2.5 or 10 $mg.mL^{-1}$ diamorphine solution in 0.1M acetate buffer at pH4; the experiments run for a maximum of 72 h. Data redrawn from Bonina et al., 1993 [67] and Barrett et al., 1993 [68].

Figure 3: Lag time and flux of phenobarbital (mean ± SD; n = 3-5) measured across preterm, full term infant and adult human skin, and through 6-9 wk hairless mouse skin. The formulation was 39 $\mu L.cm^{-2}$ of a 2 $mg.mL^{-1}$ solution of phenobarbital in ethanol. Post-application, the solvent was allowed to evaporate and the experiments run for 12h. Data redrawn from Bonina et al., 1993 [67].

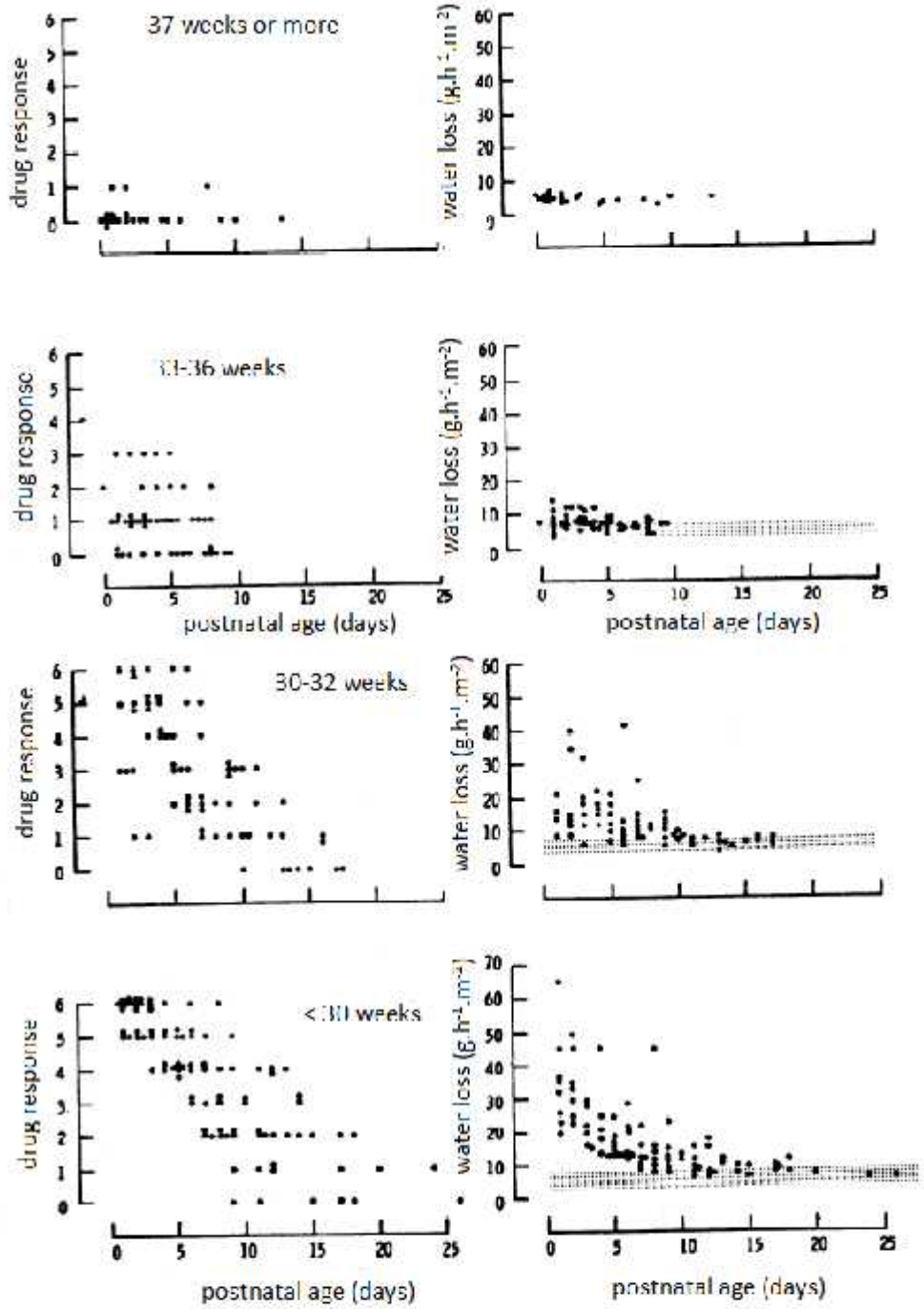
Figure 4: Schematic representation of the drug release and associated pharmacokinetic model proposed describe transdermal drug delivery in preterm infants, who lack an effective SC. The various parameters are defined as follows: V_1 and L are the volume and thickness of the drug delivery device; V_2 and L_{ve} are the volume and thickness of the viable epidermis; V_3 is the drug's volume of distribution; k_0 is the zero-order release rate of drug from the device; k_2 describes the diffusion of the drug across the viable epidermis; k_4 is the drug's elimination rate constant. The ratio $k_3/(k_0/L.c)$, where c is the drug concentration in the device, is an "effective partition coefficient". Redrawn from Evans et al. 1985 [100].

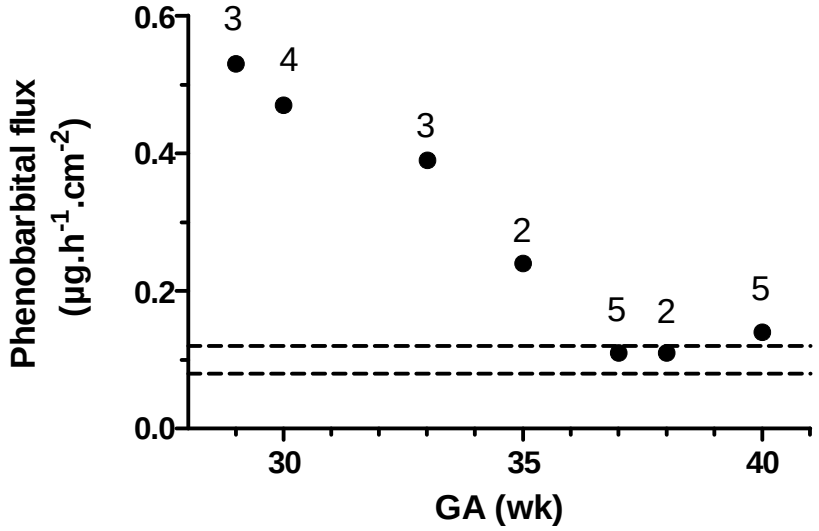
Figure 5: Passive, iontophoretic and iontophoretic corrected fluxes of phenobarbital 5 hours post-application (*left panel*), and passive and iontophoretic cumulative delivery of lidocaine after 6 hours (*right panel*) across differentially impaired skin barriers. Iontophoretic corrected fluxes represent the differences between iontophoretic and passive post-iontophoresis fluxes. Numerical values are given when too small to be visualised. Data redrawn from Djabri 2009 [105] and from Sekkat et al., 2004 [103].

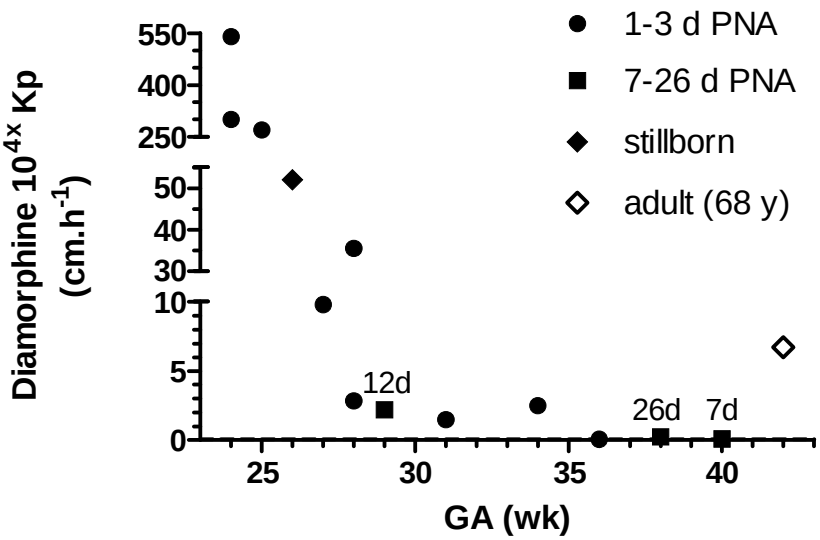
Figure 6: Fentanyl plasma concentrations measured during application (↓) and removal (↑) of a 10 cm^2 transdermal system, delivering 25 $\mu g.h^{-1}$, to 8 children aged 18-60 months. The inner and outer boxes show the mean and the standard deviation, respectively, and the whiskers indicate the highest and lowest concentrations at each time point. Reprinted from Paut et al., 2008 [114]; with kind permission from John Wiley and Sons.

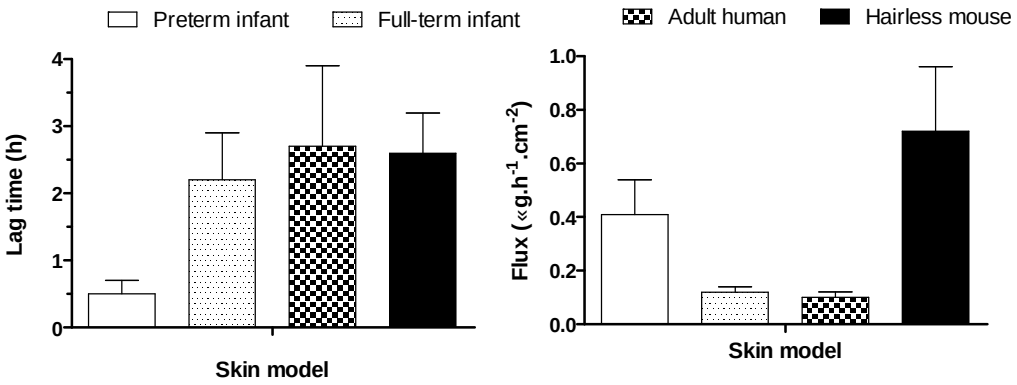
Figure 7: Tulobuterol serum concentrations and changes in peak expiratory flow rate (PEF) (mean ± SE; n=6) determined following administration of a transdermal patch to 6 (4-13 y) boys; the dose was 1 mg (< 30 kg) or 2 mg (≥ 30 kg) depending on bodyweight; the shaded area indicates the time that the patches were worn. Data redrawn from Iikura et al.,1995 [146].

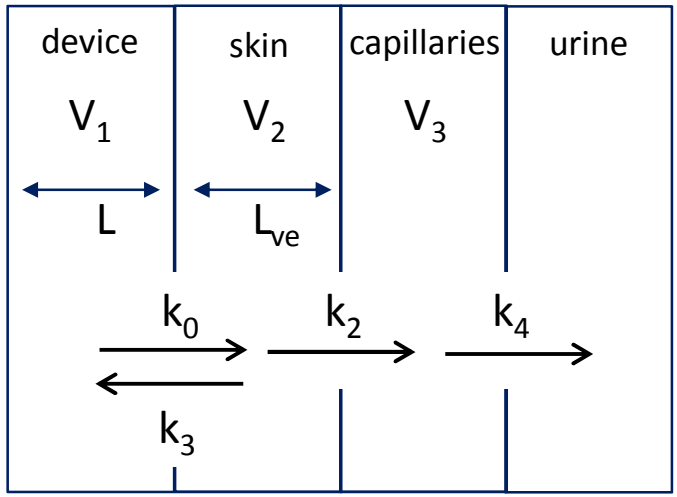
Figure 8: Schematic diagram (*left side*) and top view (*right side*) of the heated lidocaine/tetracaine Synera™/Rapydan™ patch. Pictures kindly provided by Eurocept BV and reprinted from Swayer et al., 2009 [174] with kind permission from Oxford University Press.

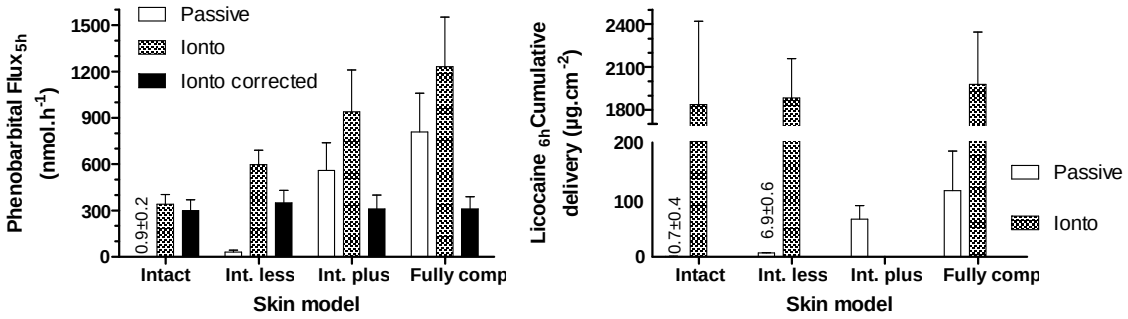

37 weeks or more
drug response
water loss (g.h⁻¹.m⁻²)
33-36 weeks
drug response
water loss (g.h⁻¹.m⁻²)
postnatal age (days)
postnatal age (days)
30-32 weeks
drug response
water loss (g.h⁻¹.m⁻²)
< 30 weeks
drug response
water loss (g.h⁻¹.m⁻²)
postnatal age (days)
postnatal age (days)

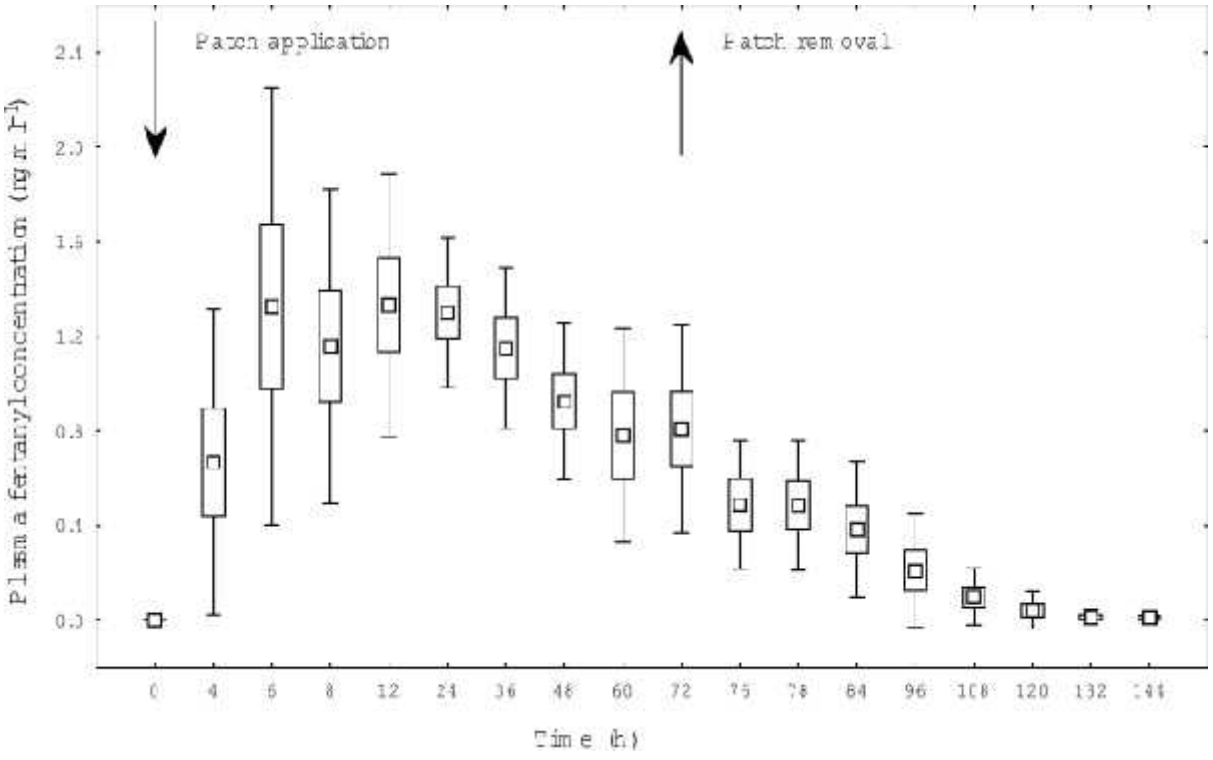

Phenobarbital flux
(µg.h-1.cm-2)
0.6
0.4
0.2
0.0
3
4
3
2
5
2
5
30
35
40
GA (wk)

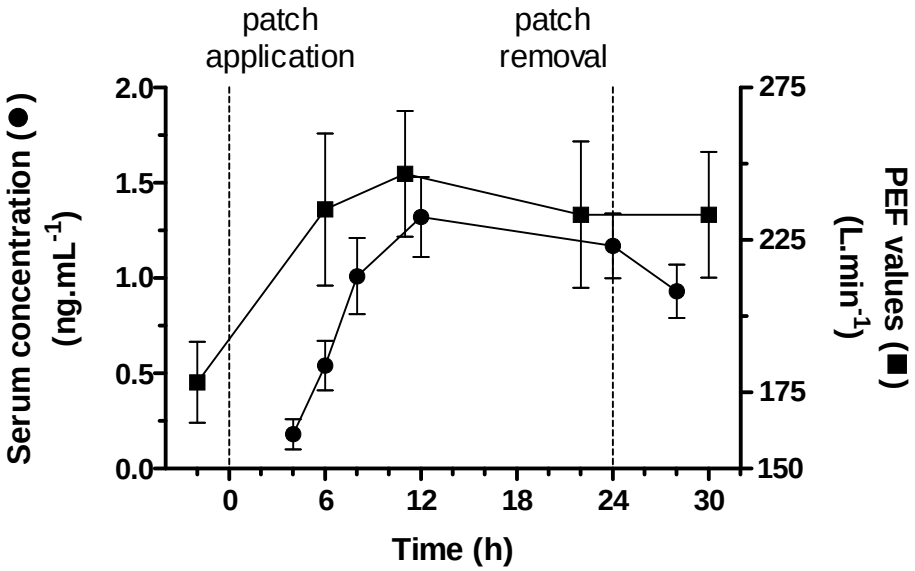

Diamorphine 10^4x Kp
(cm.h-1)
550
400
250
50
40
30
10
5
0
12d
26d
7d
25
30
35
40
GA (wk)
1-3 d PNA
7-26 d PNA
stillborn
adult (68 y)

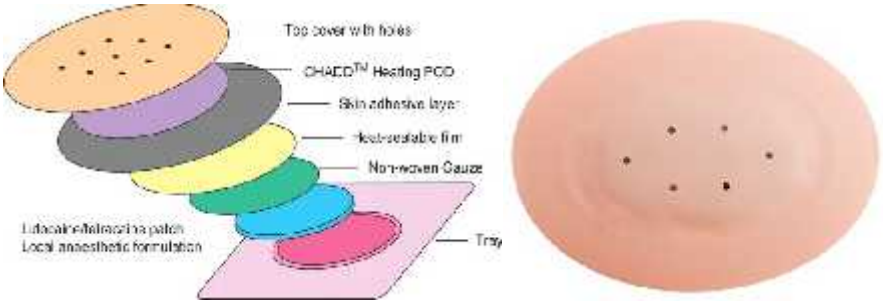

Preterm infant
Full-term infant
Adult human
Hairless mouse
Lag time (h)
0
1
2
3
4
Skin model
Flux («g.h-1.cm-2)
0.0
0.2
0.4
0.6
0.8
1.0
Skin model


device
skin
capillaries
urine
V1
V2
V3
L
Lve
k0
k2
k4
k3


Phenobarbital Flux5h (nmol.h-1)
Passive
Ionto
Ionto corrected
1500
1200
900
600
300
0
0.9±0.2
Intact
Int. less
Int. plus
Fully comp
Skin model
Licocaine 6h Cumulative delivery (µg.cm-2)
2400
2100
1800
200
100
0
0.7±0.4
6.9±0.6
Intact
Int. less
Int. plus
Fully comp
Skin model
Passive
Ionto


Patch application
Patch removal
Plasma fentanyl concentration (ng/mL)
2.4
2.0
1.6
1.2
0.8
0.4
0.0
0
4
6
8
12
24
36
48
60
72
76
78
84
96
108
120
132
144
Time (h)


patch
application
patch
removal
Serum concentration (●)
(ng.mL-1)
PEF values (■)
(L.min-1)
2.0
1.5
1.0
0.5
0.0
275
225
175
150
0
6
12
18
24
30
Time (h)


Top cover with holes
CHAEDTM Healing PCO
Skin adhesive layer
Non-woven Gauze
Tray